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AIR-BORNE INFECTION. THE RATIONALE AND MEANS OF DISINFECTION OF AIR*

STUART MUDD

Department of Bacteriology, School of Medicine
University of Pennsylvania, Philadelphia, Pa.

"THE prevention and control of acute disease of the respiratory tract is the most serious problem and at the same time the most urgent challenge that today confronts medicine in general and industrial medicine in particular. Although diseases and injuries of occupational origin have long claimed the chief interest and attention of physicians in industry, it is now well established and generally recognized that in their frequency and importance non-occupational diseases far outweigh those conditions which arise from industry. The latter are chiefly responsible for stupendous losses in both time and money to employer and employee alike."

The sentences quoted opened an address by George Morris Piersol[1] at the Third Annual Congress on Industrial Health in January, 1941.

The acute respiratory infections are of course a challenge in family

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and military practice quite as much as in industrial medicine. Because quantitative data are available for industry, however, it will be convenient to examine the consequences of respiratory disease with particular reference to industrial disability. Does examination of available data on industrial disability due to acute respiratory disease indicate that this challenge is being met in current practice? Quite the contrary. The frequency of sickness and non-industrial injuries causing disability for 8 consecutive calendar days or longer among a very large sample of industrial workers over the years 1933-1943 has been analyzed by the U. S. Public Health Service.[2,3] Sickness absenteeism among males due to respiratory disease has shown a steadily mounting rate since 1938; the rate for 1942 was higher than in any previous year of the ten-year period, 1933-42. For females the rate was steady from 1939 through 1942 but at a high level. In 1943[3] there was further striking increase in frequency of the respiratory group of diseases, the male and female rates being 61 and 57 per cent in excess of the corresponding rates for 1942, and 78 and 58 per cent in excess of their 10 year means, covering 1934-43. In the first two quarters of 1944 respiratory disease rates were just below their values for the corresponding quarters of 1943. Influenza and grippe; bronchitis, acute and chronic; pneumonia, all forms and "other respiratory diseases," including colds, sinusitis, laryngitis, pleurisy, asthma; and "respiratory infection" are chiefly responsible for the excessively high total rate.

This high and mounting rate of industrial disability from respiratory disease has been maintained during the years of the present war in opposition to the long range trend in respiratory disease mortality rates; this trend, with the notable exception of the years of the first World War and influenza pandemic, has been downward since 1900.

Whatever are the causes of this increasing rate of industrial disability due to respiratory disease, common sense cautions us not to seek the complete explanation in the conditions of work in industrial establishments alone. The packing of industrial and other workers in the ill-ventilated common carriers, trains, street cars, and busses, since rubber and gasoline shortages have been over-taxing already taxed transportation facilities, certainly provides one superlative opportunity for the spread of endemic and epidemic respiratory disease; crowded and confined places of amusement provide another.

In attempting to form even a rough estimate of the cost of this

industrial disability, recourse may be had to smaller samples which have been subjected to more detailed analysis. Figures for a public utility for the period 1938-1942, inclusive, have been published;[4, 5] these show that days lost from respiratory disease are more than a third of the total days lost from all causes of disability. The absences lasting one calendar day or longer in a sample comprising about 2,500 male and 550 female employees in a public utility in 1942, yielded an average loss due to respiratory disease for males of 3.1 days, for females of 4.3 days. It is of course understood that the figures for one company cannot be taken as representative of conditions in American industries as a whole. These rates may be either too high or too low. To gain an idea of the approximate cost, if these rates were representative, however, we may multiply these rates by the numbers of non-agricultural workers in the United States; these were approximately 26 million male and 14 million female workers. This yields an approximate total (with the reservations mentioned) of over 80 million man-days and over 60 million woman-days (or over 140 million person-days) lost to industry in the United States through respiratory disease in 1942. On the basis of 300 working days per year, this waste is approximately equivalent to the time of 470,000 persons working for a year.

The Bureau of Labor Statistics publishes monthly data on straight-time hourly earnings for manufacturing industries in the United States as a whole.[6] The author has computed an average daily earning by multiplying the straight-time hourly earnings (80.5 cents) by 8, the normal working day in American industry.* On this basis the loss in wages due to respiratory sickness amounted to roughly $900,000,000 per annum. This does not include the expenses for medical care, overhead expenses arising out of idle machinery and interruption in production schedules, and other items.

The figures above are for 1942; it has already been indicated that respiratory disease rates in American industry in 1943 were even in excess of those in 1942.[3] The average number of days lost from respiratory diseases in the above public utility during 1943 was for males 4.5 days and for females six days.[7] The estimates for June 1943 of the number of employed non-agricultural workers in the United States[8]

* It is unfortunate that daily rates of pay are not available. Since the figure representing costs of time lost due to respiratory disease is at best only an approximate one the straight hourly earnings (excluding overtime earnings) are multiplied by 8 to secure a daily wage. It is recognized that this is somewhat arbitrary.

were: males, 28.6 million, and females, 15.6 million. Calculated on the same basis as above these data yield an approximate total of 128 million man-days and 93 million woman-days or over 220 million person-days lost to industry in the United States through respiratory disease in 1943, equivalent to a waste of the labor of about 740,000 persons working for a year. The cost calculated as above would be almost 1.5 billion dollars.

Although the desirability of ameliorating disease responsible for so great a wastage in time, money and well-being would seem to be self-evident, this desirability has been questioned, notably in the interesting volume on "Air-Borne Infection" by Dwight O'Hara,[9] from which we quote:

"From a sufficiently detached and objective point of view it is possible to look upon the present prevalence of respiratory infection with some satisfaction and equanimity, for it is more responsible than any other factor for keeping the population ready and resistant to that greatest cold—pandemic influenza—which might otherwise be a much more frequent and deadly visitor . . . the writer prefers to think of them (the costs) as a reasonable price paid for the preservation of some semblance of respiratory resistance, for an initial resistance to invasion may be cheaper to maintain than to dispense with, biologically as well as socially and politically. . . . Let us not be too impatient with our yearly colds: they keep us from becoming immunologically soft, as we assuredly do when we successfully isolate ourselves from them for any long period."

However, influenza virus of Types A and B are currently each being used successfully for active immunization against epidemic human influenza of corresponding type. Cross protection is not demonstrable between types A and B. The causal agent of pandemic influenza is unknown. The justification for assuming that the miscellaneous and miserable respiratory episodes of the winter months afford protection against pandemic influenza is therefore not apparent to the present writer. Certainly we would not do well to rely upon such haphazard means. It seems to the writer more likely, indeed, that the emergence of pandemic influenza is preceded by the appearance somewhere in the world of a mutant virus of peculiarly high communicability. In this case the prevailing conditions permitting universal dissemination of respiratory flora are less a safeguard than an invitation to disaster.

Against what, then, might we become "immunologically soft", lacking the banal respiratory infections? There is evidence that the virus or viruses of the common cold do afford some transient increase in resistance, but this does not last for most persons even through a single winter, and can hardly be regarded as of long range value. Is it against the common bacterial secondary invaders, pneumococci, hemolytic streptococci, influenza bacilli or staphylococcus? Protection against invasion by each of these bacterial species is known to be specific for type, and fifty odd types of pneumococci,[10] forty odd types of *Streptococcus pyogenes*[11] and at least six types of *Hemophilus influenzae*[12] are now recognized. It is possible that a useful degree of resistance against the prevailing flora might be built up temporarily within an isolated population, such as that on a ship at sea, but in ordinary life, with innumerable opportunities for interchange of respiratory flora at work, on the way to and from work, and in homes and places of recreation, there seems to be little bacteriological or immunological basis for expecting benefit from infection. Moreover the respiratory pathogens are not well adapted to propagation or even long persistence on normal mucous membranes. Reduction of the means of dissemination of pathogens would unquestionably result in a reduction of morbidity, and a corresponding reduction in carrier rate and in the prevailing prevalence of infectious agents.

Nor do relevant epidemiologic facts sustain the argument against suppression of the vehicles of respiratory infection. Rates of respiratory disease, as is well known, tend to show a lesser early winter and a greater late winter peak. The early winter peak doubtless reflects renewed exposure of a population with a diminished resistance against certain pathogens, but the peak in the late winter or early spring is characteristically higher both with respect to morbidity and to severity of complications, and this unquestionably reflects the widespread dissemination during the winter of viral and bacterial pathogens. Finally there is the actual record showing a steady building up of rates of respiratory infection from 1938 through 1943, contrary to the long range trend. If an effective resistance were purchasable at the price of frequent infection, this should automatically check the rise in infection rates. Infection rates on the contrary have continued upward even at an accelerating pace under conditions in the war years.[3]

Carrying the thought further, it seems unlikely, too, that abolition

of water sanitation or pasteurization of milk would be advocated on the grounds that these measures make us "immunologically soft" with respect to intestinal infection (although T. E. Lawrence in his *Seven Pillars of Wisdom* does smile at the expense of newcomers to Arabia because they cannot drink with impunity from desert water holes). Vaccination can keep the immunologic mechanism in function, if necessary, more surely and more systematically than can haphazard natural infection.

'Sufficient unto the day is the evil thereof." The evils of respiratory infection are unequivocal; in the author's belief the means of dissemination of respiratory disease agents should be attacked whole-heartedly, uninhibited by concern over remote possibilities should we succeed beyond our hopes. In fact what is done in the next decades to understand and control air-borne infection may be taken as a significant index of how well we have learned one lesson of the war, that the broadest possible development of pure and applied science is fundamentally related to national security and well-being.

Relationship Between Respiratory Disease and the Infectiousness of Air

Persons sneezing, coughing, or even speaking loudly expel into the air large numbers of minute droplets which may contain in a viable and infective state any pathogenic bacteria or viruses present in their oral secretions. The larger of these potentially infectious droplets have a flight range of about a meter; they are conspicuous, are easily recoverable on bacteriological plates, and their ability to transmit respiratory infection is obvious. When droplets or sputa have dried on solid surfaces their residues may become the source of infective dust.

The role of droplets was notably stressed by the German hygienist Flügge in 1897,[13] and the doctrines of "droplet-infection" and dust-infection, or transmission of respiratory infection by droplets and by infective dust dominated thinking in regard to respiratory disease for thirty years.*

The greater part of the potentially infective material expelled by persons into the air, however, is not contained in droplets visible without special means, but in smaller droplets which evaporate almost in-

* Actually, however, Flügge himself appreciated the importance of invisible droplets accompanying the coarser visible droplets; these he recognized may persist in air for hours and reach distant parts of enclosed spaces.

stantaneously. The basic experimental demonstration was made by Wells[14, 15] in 1933-1934 that much of the enormous germ-load conveyed to the atmosphere by the evaporated residues ("droplet-nuclei") of these finer droplets, remains viable for hours or even days in the air of enclosed spaces and is wafted about like smoke to convey pathogenic bacteria or viruses to those who share the confined air.

The atomizing of mouth and nose secretions into the air has lately been revealed with dramatic vividness by high-speed photography.[16, 17] Many such photographs analyzed by Jennison showed in each sneeze about 20,000 droplets, ranging in size from about 10 μ to about 400 μ; between 40 and 80 per cent of these droplets were estimated to have diameters less than 100 μ and hence to be of the size which evaporated in the air to form potentially infective "droplet-nuclei." Photographs of sneezes through surgical masks of increasingly fine mesh show increasing efficiency in screening out droplets. Other pictures suggest that conscious effort in stifling a sneeze with handkerchief or even with the hand can materially reduce the germ-load conveyed to the air and the resultant public health hazard. Contamination of the air is not limited to sneezes, as is illustrated by photographs which show the droplets resulting, respectively, from a cough and from enunciating loudly the consonant *F*. Jennison's analysis shows that coughing or loudly speaking the consonants F, P, T and S may produce from a few dozen to a few hundred droplets. The subject has been comprehensively reviewed by Jennison.[16, 17]

The enormously important role of pathogens floating in confined air in the dissemination of respiratory disease has now been adequately documented by animal experiments, by observations in controlled human environments, and by epidemiological deductions; the evidence to 1941 has been conveniently assembled in the volume *Aerobiology*, published by the American Association for the Advancement of Science with the aid of the Committee on Aerobiology of the National Research Council.

Any attempt to appraise current progress in the sterilization of air must, however, take account of the historical background. Members of the medical profession who now occupy responsible positions in practice, in teaching and in administration have been thoroughly trained in the doctrine of "droplet-infection." Recognition of the greater importance of true air-borne infection has only come within the past ten

years, and has deeply impressed only the relatively small number of those who have seriously examined evidence which is either very modern or very old; (of course important foundations of the germ theory of disease were laid by the studies of Pasteur, Tyndall, and others on microörganisms in the air). Lack of a more insistent demand on the part of the medical profession for practical solution of the problems of air-borne infection might seem incomprehensible if this background were lost sight of. Lacking adequate demand by many prominent members of the medical profession for progress in securing pure air supplies, hygienic practices, as well as social customs, from the standpoint of health at least, have somewhat neglected the main point. The point is that, just as intestinal disease has in considerable measure been controlled by reducing the germ-load of water and milk, for the control of air-borne respiratory disease practical measures for reducing the germ-load of confined air must be instituted.

The technical devices used for quantitative estimation of the germ-load of air are currently subjected to critical comparison by du Buy and Hollaender.[18, 19] Determination of the number of microörganisms in a given air volume is performed by samplers which follow one of two principles: impingement on solid media or atomization in liquid media. The group of atomizing devices gave bacterial counts from 10 to 30 times higher than the impinging devices. Analysis of this difference showed that it was mainly due to the fact that air-borne microorganisms may occur in clusters; each cluster is counted as one colony in the impinging devices but the clumps are more or less broken up in the atomizing devices. The authors recommend that:

"Information on the manner in which microörganisms occur in a certain airspace should therefore cover the following points:

1. The total number of organisms present, singly or in clusters. An approximation to this number is given by the atomizing devices.

2. The number of particles or droplet nuclei, which contain microorganisms, either singly or in clusters, and which remain suspended in the air or are in the process of settling. This number is approximated by the impinging devices.

3. The number of particles or droplet nuclei, containing microorganisms, which are heavy enough to settle through gravity. The open plate method supplies this information."

Continuous Disinfection of Air

Effective continuous disinfection of the air of enclosed spaces has already been shown to be practicable where conditions are favorable and where the problem is approached with adequate determination and technical facilities and skill. The practical means are physical (ultra-violet radiation,[15, 20] dust-suppressive measures[21, 22]), and chemical (germicidal vapors[23, 24, 25]). Doubtless physical and chemical means will each find appropriate place as mutually complementary measures in the fully matured art of providing non-infectious air in our future homes, transport vehicles, and places of work and recreation. *Ultra-violet Radiation.* Application of ultra-violet radiation to disinfection of air has been systematically reviewed in the A.A.A.S. volume on *Aero-biology*. The physiological and the germicidal effects of ultra-violet radiation, and the characteristics and standardization of commercially available ultra-violet sources are presented in detail. Successful application of ultra-violet irradiation to reduction of wound infections in the operating room are presented by Deryl Hart, the pioneer in this field, and by Kraissl and Wilson of Columbia. Cross-infections in hospital wards and in children's nurseries and schools are reviewed and analyzed, and success in reduction of these cross-infections by appropriate use of ultra-violet irradiation is recorded. More detailed analyses of successful control of childhood contagions in schools have been published by Wells, Wells and Wilder,[26] and by Wells and Wells.[27]

More recent records of germicidal action against bacteria and viruses by ultra-violet radiation in a children's hospital, with reduction in cross-infection, have been published by Robertson, Doyle, and Tisdall,[28] by Sommer and Stokes,[29] and Henle, Sommer, and Stokes.[30] The Council on Physical Therapy of the American Medical Association has found ultra-violet lamps acceptable as an adjuvant in the disinfection of air,[31] and commercially available burners and fixtures of several types have been approved by the Council[32] for use in the operating room, hospital nursery, and hospital ward.

The statement of the Council on Physical Therapy on acceptance of ultra-violet lamps for disinfecting purposes contains carefully considered appraisal of the present status of the practical art. Pertinent statements are quoted below:[31]

"At the present juncture the design and installation of ultra-violet

lamps in their fixtures for disinfecting purposes is empirical and the adequacy of disinfection by any given installation of lamps must be judged by clinical experience. For example, clinical evidence has been submitted to the Council showing that, in a scarlet fever ward (size about 60 by 27 by 11 feet) containing sixteen cubicles, four lamp units, each one emitting a radiant flux of 30 microwatts per square centimeter at 1 meter, were found inadequate; but eight lamp units in the ward, each unit protecting two cubicles, and a ninth unit at the entrance, prevented cross-infection. This is a rather high intensity (requiring twenty minutes calculated time to produce a minimum perceptible erythema) incident on a person of average height, standing directly under a lamp fixture suspended from a ceiling of average height. A greater number of lamps, each one of lower ultra-violet intensity (say 20 microwatts per square centimeter at 1 meter) and lower power input, more evenly distributed throughout the room should be safer and equally efficient in disinfecting the air. This is a matter of engineering design, beyond the scope of the Council's purview.

"Since the ultra-violet emission from the low vapor pressure mercury discharge tube is practically homogeneous radiation of wavelength 2,537 Å, such a lamp can be readily calibrated in absolute value and used as a standard. The intensity at 1 meter may be only one-fifth of the Council's unit, or 20 microwatts per square centimeter, for safety to the occupants. This will require a minimum exposure of two hundred and fifty to five hundred seconds for adequate disinfection, which will depend on the rate of circulation and average distance of the air in front of the lamp. Evidence has been submitted to the Council showing that cross-infection in a contagious ward may be prevented by using a sufficient number of lamp units, each unit having an intensity of 30 microwatts per square centimeter at a distance of 1 meter from the burner. This will require an exposure of one hundred and sixty-seven to three hundred and thirty-four seconds for adequate disinfection, which implies a slow movement of the air in front of the lamp installation.

"The use of ultra-violet radiation for disinfecting air in industrial plants, barracks, school rooms, assembly halls, refrigerators and so on also appears to be outside the Council's purview. In fact, at this juncture the whole question of the use of ultra-violet radiation for disinfecting purposes is too complex and too little understood for the

Council to do more than attempt to keep the medical profession informed regarding particular ultra-violet lamps that are acceptable for use in this method of disinfecting air in hospitals, nurseries and operating rooms (relatively free from dust) as practiced by present day empirical methods."

It must be emphasized that the Council's acceptance statement does not prejudge the applicability and the usefulness of ultra-violet radiation to the problem of disinfecting the air of industrial plants, offices, assembly halls, railroad cars, etc. It emphasizes, however, that the specifications of engineering design and other features determining the adequacy and safety of the practical art must be further developed and applied before evaluation will become possible.

Another paragraph of the Council's statement discusses responsibility for design of installations.

"It is to be noted that a lamp used for disinfecting purposes is a single unit in an installation, and that compliance of the ultra-violet output of a single lamp unit with the Council's requirements does not insure adequate radiant disinfection or the safety of the occupants of the room in which an installation of such lamps is in actual use. Obviously the manufacturer and distributor of such lamps must assume some responsibility for the adequacy of the lamp installation for purposes of radiant disinfection of the air and for the adequacy of the protection from injury of the occupants of the space irradiated. Concerning these questions the Council cannot undertake supervision or assume responsibility for the satisfactory performance of any particular installation."

The Senior Biophysicist of the Division of Industrial Hygiene, National Institute of Health, (who also is Referee for the A.P.H.A. on Disinfection of Air by Ultra-Violet Irradiation), has critically reviewed applications, precautions, and limitations of the use of ultra-violet irradiation to disinfection of air.[33, 34] The statement of the Council on Physical Therapy is quoted with approval: "Obviously the manufacturer and distributor of such lamps must assume some responsibility for the adequacy of the lamp installation for purposes of radiant disinfection of the air, and for the adequacy of the protection from injury of the occupants of the space irradiated."

Acceptance by the architectural and engineering groups in whose province air hygiene may be considered as properly falling, of a measure

of responsibility for elaborating specifications for proper design and servicing of installations would be an important step toward development of a practical art of air hygiene. In this connection it is encouraging to note the recent formation of a Technical Advisory Committee on Air Sterilization and Odor Control of the American Society of Heating and Ventilating Engineers.[35]

The efficacy of ultra-violet irradiation in killing air-borne bacteria and viruses under conditions in which the air is relatively free from dust and lint has been confirmed in Great Britain by Andrewes and others[36] and by Edward, Lush, and Bourdillon.[37] The difficulty of disinfecting dust-laden air by this means has also been emphasized. Andrewes *et al.*[36] suggest the combination of air filtration and ultra-violet irradiation in recirculation systems and for certain special purposes.

Complete success in controlling the spread of a specific air-borne disease under rigid experimental conditions has recently been recorded by Lurie.[38] A rabbit colony, 73 per cent of whose unprotected control animals developed progressive tuberculosis, was completely protected from tuberculosis by ultra-violet irradiation over the period of the experiment (almost a year). The author concludes:

"The contagion of tuberculosis in these studies is air-borne and the radiant energy exercises its protective influence by its bactericidal properties. It is probable that ultraviolet irradiation may control air-borne contagion of human tuberculosis."

A factor of critical importance in determining practical success or failure is illustrated by recent experiences relating to control of colds. The Cradle Society in Evanston, Illinois, erected in 1939 a new building specifically planned in reference to controlling respiratory infection.[39] Infants are cared for from shortly after birth until adoption. The normal infants receive care under strictest nursing precautions in wards of three types: (1) units provided with modern air-conditioning but (from 1939 to 1942) without additional protection, (2) similar air-conditioned units protected from air-borne infection by ultra-violet irradiation of the barrier type designed by W. F. Wells, (3) air-conditioned units protected by special mechanical means designed by J. A. Reyniers.

Primary introductions of colds into the institution occurred through nurses contracting colds and by admission of new infants with colds. Infections contracted from these infected sources were for three years

TABLE I

INCIDENCE OF RESPIRATORY INFECTIONS AT THE CRADLE

	Period from April 1, 1939 to March 31, 1942			*Period from April 1, 1942 to September 30, 1944*	
	Number of Primary Infections	*Number of Secondary Infections*		*Number of Primary Infections*	*Number of Secondary Infections*
Control Unit without germicidal lamps	43	21	Control Unit with germicidal lamps	39	2
Wells Unit	45	1	Wells Unit	40	1
Reyniers Unit	49	1	Reyniers Unit	46	3

This table is published here through the courtesy of Iwan Rosenstern.[40]

practically limited to the air-conditioned control units, as shown in Table I.[40] At this time it seemed no longer justifiable to continue the air-conditioned units without further protection and ultra-violet burners of the wall-bracket type for upper-air irradiation were installed in the control wards. Since then secondary respiratory infections have been negligibly few in all units. Bacteriological studies by Iwan Rosentern[39, 40] of the air of the several units under various experimental conditions have been entirely in harmony with the clinical results.

In contrast to these successful results in controlling the spread of colds among fully institutionalized infants is the experience with colds in primary schools recorded by Wells, Wells and Wilder.[26] These investigators were successful with ultra-violet irradiation in controlling childhood infections whose source of contagion is in school, but unsuccessful in controlling colds, presumably because there was adequate opportunity to contract the colds in unprotected environments outside the school, as shown by a uniform daily incidence of colds throughout the week.

The critical importance of proper design and adequate intensity of irradiation has been illustrated in a current study of the control of air-borne infection in a naval training station at Sampson, New York.[41] Two sets of barracks were equipped with burners arranged to irradiate the air of the barracks above eye level and the floors with ultra-violet radiation. One set of barracks received radiation of relatively high in-

tensity, the other of relatively low intensity. Average intensities in both cases, however, were not higher than the levels set by the Council on Physical Therapy; the high intensity exceeded the low intensity level by less than two-fold. Similar barracks were maintained as unirradiated controls in each case. Exceedingly careful epidemiological analysis showed that the ultra-violet irradiation of high intensity was accompanied by a statistically significant reduction of 25 per cent of respiratory illness, whereas respiratory illness in the low intensity barracks did not differ significantly from that in the unirradiated controls.

In view of the critical importance of proper design of ultra-violet installations in governing adequacy and safety, it is fortunate that significant progress is being made in the formulation of specifications. Notable advances in this respect have recently been reported by Wells[27] and by Buttolph.[42] Although these matters are in the field of engineering and outside the scope of this lecture, their importance in determining the success or failure of the practical art of air sanitation can hardly be overemphasized.

Germicidal Vapors. The spraying of germicides into the air was of course a part of the technique of antiseptic surgery. Modern interest in germicidal mists was stimulated by the demonstration by Douglas, Hill, and Smith,[43] Trillat,[44] and Masterman[45] that certain bactericidal substances, e.g. NaOCl and a number of phenolic compounds, when dispersed in the air as fine mists or aerosols exerted a highly lethal effect on air-borne bacteria. Twort, Baker, Finn, and Powell[46, 47] found that hexyl-resorcinol dissolved in propylene glycol made a highly effective and satisfactory aerosol.

An inclusive and practical discussion of the problems of air-borne infection and means for its amelioration in war-time Britain has been presented by Andrewes and others.[36] Concerning germicidal mists and vapors they conclude:

"*Hexyl-resorcinol* in propylene glycol has proved perhaps the most effective under laboratory conditions, but unfortunately neither the antiseptic nor its solvent is at present readily enough available* in large amounts to warrant its introduction except for special purposes."

Considerations of economy and practicability as well as of efficacy have served to focus attention in Britain on the germicidal value of

* Hexyl-resorcinol is at present available in limited amounts and the glycols are available in large amounts in the United States.

hypochlorites and hypochlorous acid. Actually the use of hypochlorites for purification of air was first tried in England as early as the influenza pandemic in 1918. Masterman[48] reviews in detail the early history and various controversial aspects of the use of hypochlorites for air purification. He describes an atomizing device (Dynalysor) as already in successful operation. "For many months the Dynalysor has been successfully employed for hypochlorite spraying in hospitals, offices, and other inhabited rooms, and air purification by hypochlorites is not a scheme 'with definite possibilities' but a successful *fait accompli*." Masterman concludes that HOCl gas is the active germicide in hypochlorite spraying.

Bourdillon, Lidwell, and Lovelock[49] have reported success with hypochlorite atomized by a hand spray in disinfecting air contaminated by sneezing. They note certain unfavorable conditions, "such as low relative humidity or high content of organic matter in the air, which may hinder the action of hypochlorite sprays." They also note promising results from vaporized lactic acid.[50]

Edward and Lidwell[51] report favorable tests on sterilization of air-borne influenza virus with hypochlorous acid gas.

"A concentration of 1 vol. of gas in 2 million vol. of air is probably effective in destroying 99 per cent or more of virus particles when the proportion of these in the air is small. Preliminary experiments on mice and cats are recorded which failed to reveal any toxic effects produced by inhaling the gas in relatively high concentrations or for prolonged periods. Acute irritation of mucous membranes only was found. This did not appear to lead to any increased susceptibility of mice to subsequent infection with influenza."

Exploration of the possibilities of continuous disinfection of air by chemical substances has made and is making rapid progress in America through the work of O. H. Robertson and his associates. They determined that certain of the glycols alone, notably propylene glycol[23] and triethylene glycol,[24] provided promising means for continuous disinfection of air. They demonstrated that the germicidal action depended, not, as earlier supposed, upon collision of fluid droplets with air-borne bacteria, but upon condensation of hygroscopic glycol molecules upon air-borne droplets containing bacteria. One gram of propylene glycol dispersed as vapor in 5 or 10 million ml. of air and 1 gram of triethylene glycol vapor in several hundred million ml. of air was found to kill

pathogenic respiratory bacteria and the virus of influenza in air in seconds or minutes. Rat and monkey colonies kept constantly in atmospheres saturated with vapors of propylene glycol for periods up to eighteen months, and triethylene glycol up to a year suffered no ill effects detectable by observation or microscopic examination[25] and the animals bore young.[52]

"The germicidal activity of glycol vapors is markedly influenced by certain environmental factors, the most important of which is atmospheric humidity. A dry atmosphere is unfavorable. Likewise desiccated bacterial particles are not as susceptible to the vapor action as are moist ones. It has been found that the glycols are most effective at relative humidities between 40 and 60 per cent."

Subsequent work by Bigg, Jennings, and Fried[53, 54] places the relative humidity for maximal germicidal action of glycol vapors at from 30 to 50 per cent. These and subsequent papers[52, 55-57] indicate the types of apparatus that are being developed for disinfection of the air of large enclosed places by glycol vapors.

Careful investigation of the possibility of fire hazard resulting from the dispersal of glycol vapors into the atmosphere of enclosed spaces has also been made by Bigg, Jennings, and Fried.[54] These authors conclude:

"In the vapor-phase concentration required for air sterilization, propylene and triethylene glycol offer absolutely no fire or explosive hazard. The addition of water to these substances greatly reduces the possible fire hazard produced by their presence in storage or vaporizing devices."

Most recently, practical apparatus[56, 57] has been constructed and utilized for introduction into the air of properly humidified glycol vapors. Boiling glycol-water solutions are maintained automatically at any desired relative concentration. The vapors emitted from such boiling solutions are of constant composition and are bactericidal. A predetermined rate of delivery and concentration of water and glycol vapor may be accurately produced by varying, respectively, the heat input and the temperature of the boiling mixture. Apparatus of this type has been given laboratory trial and also practical test in large dormitories. The authors'[57] conclusions are quoted in detail:

"Bactericidal quantities of glycol vapors can be maintained in large occupied spaces for long periods of time. It has been shown that glycol

vapors can be uniformly distributed in large rooms. A means for generating glycol vapors in controlled amounts is described. The occupants of treated rooms experience no discomfort due to glycol vapors. Triethylene glycol is preferred over propylene glycol because much smaller amounts of the former are bactericidal. Optimum bactericidal concentrations required with triethylene glycol range from 0.003 to 0.005 mg. per liter of air. Relative humidities in the range 25 to 60 per cent are required for optimum bactericidal action.

"Records were kept of the number of men from each dormitory contracting diseases believed to be air-borne. Studies of the hospital records indicated a noticeable reduction of infections in the test dormitories. The results were very encouraging and further carefully controlled observations with larger groups are being planned."

Clinical application of glycol vapors during the winters of 1941-1942, 1942-1943 and 1943-1944 are recorded by Harris and Stokes[58,59,60] working at the Children's Seashore House in Atlantic City. This convalescent home has a relatively stable population and the children in the wards are confined to their beds and thus subject to a minimum of contact or direct-droplet infection. Experimental and control wards were carefully matched; control and glycol-vapor wards were alternated for three week periods throughout the respiratory season. Ill effects were not encountered. The germ-load of the air was shown to be greatly reduced by the glycol vapors as judged by direct plate counts. In the preliminary study two respiratory infections occurred in the vapor-containing ward as compared with sixteen in the analogous control ward. During the second winter five respiratory infections occurred in the vapor-containing wards as compared with 100 in the similar control wards without glycol vapor. During the season of 1943-1944 respiratory infections were in the ratio of 6 in the vapor containing to 16 in the control wards.[60]

"The concentration of propylene glycol vapor in air was maintained in the neighborhood of one part in 15,000,000 (0.069 mg./liter). Concentrations at various times and in different parts of the experimental wards ranged from 0.048 mg./liter to 0.094 mg./liter.

"In the case of tri-ethylene glycol the maintenance of a satisfactory concentration presented a greater problem, because of the narrow range between bactericidal concentration and precipitating concentration mentioned above. In the absence of sensitive methods for regulating or

measuring concentrations of tri-ethylene glycol vapor in air, a rate of vaporization sufficient to disinfect the air to a considerable degree was often found to produce precipitation of glycol on windows, floors and objects in the ward. The concentration of this vapor in air ranged between 0.0018 mg./liter and 0.0033 mg./liter.

"The difficulties encountered in this study in the use of tri-ethylene glycol are due largely to the early stage of engineering development of the field, and to the relatively small size of the enclosed spaces involved. In a larger volume of air the fluctuations in glycol concentration caused by occasional opening of doors, etc., would be proportionately smaller and the concentration could be maintained in a narrower range. The ultimate development of devices to regulate the rate of vaporization of tri-ethylene glycol by the concentration of the vapor present in air at the moment may obviate the difficulties in using this disinfectant and permit workers to take advantage of its higher potency.

"At the present writing, however, it would appear that in the absence of refined devices to regulate the rate of vaporization of glycol, propylene glycol is the agent of choice in small wards, offices and spaces of similar size."

In his report as Associate Referee on Disinfection of Air by Germicidal Vapors and Mists, Professor O. H. Robertson writes:[61]

"Practical application of the use of glycol vapors for the purpose of controlling air-borne infection has had to await the construction of suitable apparatus for the dispersion of glycol vapors into large enclosed spaces and the development of an instrument to control automatically the concentration of glycol vapor in the air. Rapid progress is being made in the solution of both these problems."

Types of vaporizing device for large spaces,[52, 56, 57] for smaller spaces[52, 57, 62] and means for the regulation of vapor concentration[52] are in process of elaboration and trial.

Dust Suppression: Consideration of the air as a vehicle of infection would be very incomplete without reference to the importance of dust, both as a carrier of pathogenic bacteria and viruses and as a shield of air-borne pathogens against the means used for disinfection of air, such as ultra-violet radiation and germicidal vapors. British investigators[21, 36] in particular, working under wartime conditions, have found dust a very serious obstacle to application of measures for disinfection of air.

They have introduced practical methods for reducing dust from floors, textiles, and bed clothes by treatment with light paraffin oils.

Results of practical trials of the effect of suppression of dust by oiling have recently been recorded.[22] Measles, a catarrhal disease, often complicated by hemolytic streptococcal infection, affords conditions in which a patient's surroundings are particularly apt to be contaminated by streptococci which remain viable and may readily be redispersed in dust.

"An investigation into the control of dust-borne haemolytic streptococci was carried out in two measles wards of identical design during the spring of 1943. In the *Test Ward*, during a three-weeks preliminary period, the floor alone was oiled. During a subsequent nine-weeks period bed-clothes, patients' garments, and all other woolen and cotton articles in ward use were treated regularly with emulsions of technical white oil, and the floor was re-oiled at intervals. In the *Control Ward* no anti-dust measures were taken. In both wards the air was sampled for total bacteria and for haemolytic streptococci during bed-making and sweeping, and the streptococcal cross-infection and complication rates were recorded and analysed. In assessing the cross-infection rate Type 6 streptococcus was adopted as the 'indicator organism,' since in the two wards it accounted for 90 per cent of the cross-infections and for all the middle-ear complications occurring after admission.

"In the *Test Ward*, while the floor alone was oiled the Type 6 cross-infection rate was 58.1 per cent, compared with a rate of 53.3 per cent in the *Control Ward*. In each ward the middle-ear complication rate due to Type 6 was 18.4 per cent. Haemolytic streptococci were numerous in the air of both wards during bed-making, the predominant strain being Type 6. Thus oiling of floors alone was not sufficient to control the spread of dust-borne haemolytic streptococci in measles wards.

"In the *Test Ward*, while the full anti-dust measures of oiled bedclothes, garments, etc., and oiled floor were in force: (a) the mean haemolytic streptococcus count in the air during bed-making was reduced by 97.5 per cent; (b) the mean bacterial count in the air during bed-making was 91 per cent less, and the mean haemolytic streptococcus count 98 per cent less, than in the *Control Ward;* (c) the mean bacterial count in the air during sweeping was 92 per cent less, and the mean haemolytic streptococcus count 99 per cent less, than in the

Control Ward; (d) the Type 6 cross-infection rate was 18.6 per cent, while in the *Control Ward* it rose to 73.3 per cent; (e) the middle-ear complication rate due to Type 6 was 2.8 per cent, compared with 14.3 per cent in the *Control Ward.* Thus the oiling of all bed-clothes and ward-linen, in addition to the oiling of floors, effectively controlled dust-borne streptococcal infection in measles wards. Cross-infection from direct contact or mediate means was not prevented by anti-dust measures.

"A high streptococcal infection rate occurred in spite of intensive sulphonamide prophylaxis. The cross-infecting Type 6 strain was found by *in vitro* tests to be sulphonamide-resistant."

A complete and practical technique for the application of dust-laying oils to blankets, sheets and other woolen and cotton fabrics has been worked out in the laboratories of the British Launderer's Research Association.[63]

In another British study[64] the wooden floors of all barrack-rooms, sleeping huts, offices and lecture-rooms in a military training center were treated with spindle oil at regular intervals. The floors of a similar unit were left untreated as a control. Careful weekly records were kept of all men reporting sick with a respiratory infection during the seventeen weeks ending March 27, 1943. The respiratory infection rate was 7 per 1,000 men in the unit with oiled floors, 38 per 1,000 in the control unit. The oil used was non-inflammable, caused no unpleasant smell and made the floors easier to keep clean. "The regimental officers and men welcomed the oiling of the floors."

Robertson and co-workers[65] have recently reviewed the literature on dust-suppressive measures in relation to cross-infections in hospitals and military establishments. Practical means and techniques are considered in detail. A test is reported on the effect of oiling floors and bed clothes on the incidence of acute respiratory diseases among 5500 troops in the test barracks and a similar number in the control barracks over a ten weeks period. An average weekly reduction of 24 per cent in hospital admissions for respiratory disease was obtained in the treated barracks. In the test groups whose controls had a high rate of infection, average weekly reductions in hospital admissions of over 50 per cent and of dispensary visits for respiratory infections of 37 per cent, were obtained.

Experiments on the reduction of the infectivity of dust by floor irradiation with ultra-violet have been instituted by Hollaender, du

Buy, Ingraham, and Wheeler.[66] As a result of these experiments they suggest that "floor irradiation be combined with ceiling irradiation in practical tests in barracks or hospital wards to determine the effect of any ultra-violet irradiation in lowering morbidity rates or preventing cross-infection." They caution that "if such experiments be attempted it must be borne in mind that certain types of flooring may prove to be capable of reflecting sufficient amounts of ultra-violet to cause harmful effects."

Thus rationale and scientific basis have already been laid down for three independent types of measures for controlling the dissemination of disease agents through the air—ultra-violet irradiation, germicidal vapors and dust suppressive measures. Each has been shown capable, under appropriate conditions, of reducing significantly the incidence of respiratory infection. Doubtless all of these measures, singly and in combination, will find their places in the maturing practical art of air sanitation.

Studies directed primarily against the secondary reservoirs of infection in floor dust, the lint of bed clothes, etc., have for the most part used the dissemination of hemolytic streptococci as a primary criterion. These disease agents, because of their chain structure, are quick to settle out of the air, and they remain viable for extended periods. The use of hemolytic streptococci as indices, therefore, may tend to overemphasize the relative importance of dust and underemphasize the importance of droplet nuclei in the over-all picture of air-borne infection.

A recent study[67] of the seasonal patterns of certain infectious diseases indicates that methods directed against air-borne "droplet nuclei" and those directed against the secondary reservoirs of pathogens may have quite different values in respect to the suppression of different disease agents. The author concludes:

"The seasonal patterns of spread of measles and chicken pox, while differing markedly from each other, are both entirely compatible with the theory, outlined at the beginning of this paper, of transmission by air-borne droplet nuclei. . . .

"The seasonal patterns of scarlet fever, on the other hand, suggest that means of transmission less amenable to control by ventilation than are droplet nuclei play an important role in its spread."

In the total problem of control of respiratory disease, of course appropriate measures for immunization of individuals and groups, and

the emerging technique of chemoprophylaxis,[68-72] are as important as measures of environmental sanitation. However, immunization and chemoprophylaxis are outside the scope of this review.

Considered in terms of cost in money and effort when applied on a national scale, control of air-borne infection seems to present a problem of very great proportions. Relative to what it costs to leave air-borne infection uncontrolled, however, the money costs of preventive measures shrink to comparatively trivial figures. Is the effort too much to ask of a people whose energies have so long been mobilized for the purposes of war? Is not a part of any rational program of reconversion to peace the clear conception of orienting purposes whose achievement would add to national health and well-being? Is not freedom from sickness worthy of a place with freedom of worship, freedom of speech, freedom from want, freedom from fear?

Summary

Respiratory disease is responsible for more than a third of the total number of person-days lost to American industry by disability; it is of course a correspondingly serious problem in domestic life and during military training. The air of enclosed spaces is at present the principal vehicle for the dissemination of respiratory disease. The rationale of rendering air safe for human occupancy has been laid down in the laboratory and in suitable, controlled human environments. The means are ultra-violet irradiation, dust-suppressive measures, and the use of germicidal vapors of hypochlorous acid and of propylene and triethylene glycol. Elaboration of the practical art of providing safe air supplies is, however, not to be accomplished cheaply or through the efforts of a few people. A specialty or specialities in sanitary engineering will have to develop around air sanitation, as has occurred around water and milk sanitation. Physicians, air-conditioning specialists, heating, ventilating, and illuminating engineers, architects, the manufacturers of necessary equipment, agencies regulating public health practice, and the industries which will benefit by reduction of industrial disability through respiratory disease ultimately will all have to contribute effort and money to solving the manifold aspects of the problem. How much is it worth in war time to reduce an annual industrial waste equivalent to the output for a year of approximately a half million workers? How much is it worth in peace time to reduce a corresponding loss of effi-

ciency and well being from the drain of respiratory infection?

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EXPERIENCES WITH RHEUMATIC FEVER IN THE ARMY*

IRVING S. WRIGHT, Colonel, MC, AUS

Consultant in Medicine, Ninth Service Command

AN attempt to crystallize the status of experience with rheumatic fever at this time is fraught with hazard, yet such attempts seem warranted even if their main function remains but to challenge previous conceptions and to raise new questions. The opinions expressed in this paper are those of the author and are not shared by all workers in this field. They are not to be construed as representing official pronouncements of the Office of The Surgeon General.

Rheumatic fever, as most physicians knew it prior to the war, was largely an endemic disease with sporadic, but relatively rare epidemics of minor proportions. It was not considered to be highly communicable. Numerous publications contended that the major etiological factors were malnutrition, poor heating, and other problems of the underprivileged classes. By far, the majority of cases developed in children and adolescents. It has always been a potentially very serious disease for the affected patient.

It is a serious problem for the military forces, both because of the immediate long hospitalization and because of the danger of the effects which may invalid these patients for years later in life. In several areas it has assumed epidemic proportions. These have been most pronounced in camps in the Rocky Mountain and Central states. In some barracks it has reached a much higher incidence than would have been anticipated in this age group, on the basis of former experience.

The curve of incidence has, in general, diminished with increasing age. The oldest patient seen by the author, having his first attack while in an Army hospital, was 42 years of age.

The military personnel with this disease have not been emaciated, undernourished, or in poor physical condition. On the contrary, they represent, in most instances, the cream of our youth, physically and

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mentally. They are in splendid physical training. Those stricken in this country have been on plentiful diets which were, for the most part, very well planned. Some of the men who developed rheumatic fever overseas have been on field rations for from one to five months. Heavy physical exercise with resulting fatigue has been frequent, but not invariable before onset. Exposure to prolonged dampness and cold has appeared to precipitate many atacks, but again has not been an invariable prefatory occurrence.

Close contact in living quarters has been a most consistent environmental factor, as it almost invariably must be, in the spread of the disease since practically all attacks of rheumatic fever are preceded by Group A hemolytic streptococcal infections of the respiratory tract. Evidence is increasing that the lesions of rheumatic fever may be the results of an anaphylactic reaction to some foreign antigen, such as a product of the hemolytic streptococcus.[1,2] This applies to the reaction of rheumatic pneumonitis[3] as well as joint and skin manifestations.

Characteristically, in the Army camps the curve of increase in the incidence of rheumatic fever has been preceded by a curve of increased incidence of upper respiratory infections. Where bacteriological studies have been made, these have been predominantly Group A Streptococcus infections. On the other hand, many waves of upper respiratory infections have not been followed by any increase in rheumatic fever. This has been previously observed in relation to the Autumnal epidemics of "colds" along the Eastern seaboard.

In general, the Army cases have followed the usual course of events as outlined by Swift[4] namely:

Phase I.—An upper respiratory streptococcal infection, either a nasopharyngitis, follicular tonsillitis, or scarlet fever.

Phase II.—A quiescent phase, which may be considered as an incubation period, and

Phase III.—The phase of rheumatic activity, which may continue in duration from a few weeks to years.

Actually the first two phases frequently escape detection, or are quickly forgotten, so that only careful questioning will reveal even an approximately accurate rate of incidence. These two phases are, nevertheless, of greatest importance since most patients convalescing from *streptococcus* tonsillitis, or nasopharyngitis are below par physically, and being candidates for rheumatic fever and other serious diseases

should not be exposed at too early a date to too great cold, dampness, or fatigue.

The second phase may pass immediately into the third or active rheumatic fever phase, or it may take as long as six to seven weeks. Most of the serious complications can be detected by having the patients under observation between the fifteenth and twentieth days after the onset of Phase I. In military establishments this is not always feasible, but proper instructions can be issued to the soldier so that suspicious symptoms or signs developing during that time will be brought immediately to the attention of the medical officer.

The history of previous attacks has been very common. In one ward in an Induction Center Station Hospital of twenty-eight patients who had developed rheumatic fever within thirty days of their entrance into the service, eighteen had had a previous history of one or more previous attacks from one to fourteen years before. Most of these men had done fairly well in the protected environment of civilian life, but even a brief trial with exercise and exposure to which they were unaccustomed resulted in reactivation of their disease. Ten of them had no history suggestive of the first phase of upper respiratory infection.

This gives rise to the following question: Is this new attack, thus precipitated, due to hidden foci of streptococci Group A; or is it due to reactivation of a latent anaphylactic process secondary to the stimuli of fatigue, exposure to inclement weather, or upper respiratory infections, any one of which may act as the trigger mechanism initiating the process?

It has been difficult, and even impossible at times, to differentiate the pseudo from the true rheumatic fever syndrome. The confusing signs include tachycardia, substernal distress, dyspnea on exertion, pronounced arthralgia, and backache, without local redness, heat, or swelling of the soft parts. If not due to true rheumatic fever, these are usually considered to be on the basis of toxicity (though we do not know exactly what we mean by that term), and disappear with the general improvement of the patient.

Most of the patients in the military services have followed the usual course during the active rheumatic fever phase. Several points, however, are worthy of note. In more than 1000 patients, there have been only three who have had chorea at any time, during their Army serv-

ices. In no case has it occurred as an isolated manifestation of rheumatic fever. This is remarkably lower than the incidence of chorea in rheumatic fever in pre-war civilian practice.

The characteristic painful, swollen, red, hot joints have varied greatly in shifting tendencies and in severity. The cardiac manifestations have included precordial discomfort, tenderness on pressure, pain, dyspnea, tachycardia, premature contractions, fibrillation, and flutter. Heart block varied from partial to complete with ventricular rates as low as 20 per minute. This will be discussed later in this paper.

The hearts have rarely been slightly enlarged with the first attack. On auscultation the first sign of change has most frequently been a muffled soft *systolic blowing murmur* over the mitral area with a fairly wide distribution. This has frequently disappeared on change of position such as sitting upright, and may disappear completely with subsidence of the acute phase of the disease, in which case it may be difficult to be certain whether it was evidence of an organic or functional process. Although the fashion of the day is to arbitrarily classify many such murmurs as functional, it would seem advisable to be less positive since the post-mortem findings have embarrassed the clinician more than once in this regard. *Diastolic* and *presystolic* murmurs in this area are more safely classified as organic. In some instances, a *mid-diastolic rumbling murmur* has developed two to three months after the initial rheumatic fever attack. Several of these have later become inaudible. The explanation for this is not clear. The most common *murmur in the aortic area* has been soft, blowing, and *diastolic* heard loudest over the second and third right interspace. It probably represents a relative insufficiency in the majority of patients and frequently, but not always, disappears. The murmurs of mitral and aortic stenosis tend to develop later, and were with few exceptions, encountered only in patients with previous history or evidence of rheumatic fever.

Pericarditis, while not common, has occurred frequently enough to be worthy of constant consideration. Most of these patients developed their pericardial signs within a few days of the onset of the active rheumatic fever phase, often before therapy had reached an intensive phase. The lack of reliability of statistical studies in this regard was recently brought forcibly to my attention by the following incident: Two hospitals drawing from the same pool of personnel each had approximately seventy-five patients with rheumatic fever. One had no

patients with pericarditis, the other had eight patients with pericarditis. In each of these the pericarditis developed within the first four to five days of onset of recognized rheumatic fever.

Heart failure has been very rare during the first attack, having been encountered in only five patients in this series. Changes in the electrocardiogram will be discussed below.

It must never be forgotten that abdominal symptoms may represent the onset of rheumatic fever. Pain, tenderness, rebound tenderness, and cramps have been frequent and have led to confusion with the diagnosis of appendicitis.

Of particular note has been the scarcity of subcutaneous nodules—only four examples have been seen in more than 1000 cases. Purpura has been rare. The reason for this is not understood. Of possible significance in this regard is the recent work of Link[5] and others demonstrating that salicylates may produce hemorrhage. This occurs only in the presence of a Vitamin K deficiency and is prevented by adequate Vitamin K in the diet. This may, in part, explain the tendency toward hemorrhage noted in underprivileged children and its absence among well nourished troops. It has further been noted[5] that sodium salicylate, which is used in the Army, produces less tendency toward reduction of the prothrombin level than acetyl salicylic acid—commonly used in civilian practice.

We have seen eight examples of cerebral manifestations; five simulating meningitis and three developing a transient psychosis. In these three the question of salicylism was considered. In this series, there have been seven fatalities. Two were associated with pericarditis, and five with heart failure. All of these had histories of previous attacks of rheumatic fever. Four of the latter five had pneumonia which, in two instances, was shown pathologically to resemble rheumatic pneumonitis as described by Rich and Gregory.[3] Numerous additional patients developed what was diagnosed as primary atypical pneumonia, but which was probably in some cases, rheumatic pneumonitis. This possibility should be constantly kept in mind in treating patients with rheumatic fever.

Electrocardiographic changes have been of great interest. The most consistent change was prolongation of the P-R interval—the longest seen being 0.62. This finding is often the only evidence of heart involvement and is usually transient, disappearing in from one to six

months. Partial A-V heart block with the Wenckebach phenomenon and dropped beats has occurred in approximately 6 per cent of the cases. Auricular ventricular dissociation has occurred with equal frequency.

Prolongation of the P-R interval was found in fifteen out of two hundred patients suffering from what was considered to be typical rheumatoid arthritis, at the Army and Navy General Hospital. Aschoff bodies have been found in the hearts of many patients who died after years of so-called typical rheumatoid arthritis. The prolonged P-R intervals added additional evidence to the hypothesis that, in many instances, these diseases are closely related or run concurrently in susceptible individuals.

The question inevitably arises as to whether we are detecting all of the changes which takes place in the heart. Wendkos[6] has contributed suggestive information to this field by the following study: Eight men suffering from acute migratory polyarthritis (typical of rheumatic fever), in whom no evidence of heart damage existed, showed normal electrocardiographic tracings. Immediately after a controlled tracing, 0.5 Mgm. of ergotamine tartrate (a sympathicolytic drug) was injected intravenously in each. Further tracings were recorded thirty and sixty minutes after injection. Additional tracings were taken of five patients after all evidence of activity of the disease had subsided. The results were as follows: The control tracings in each instance were normal. In six of the eight cases the tracings taken after the injection of ergotamine showed significant disturbances in rhythm usually associated with rheumatic fever, consisting of first degree A-V heart block in four instances, second degree A-V heart block with dropped beats in one instance and nodal rhythm with first degree A-V block in another. The maximum effect was noted in thirty minutes and the effects had generally disappeared within sixty minutes. In the five individuals, who were rechecked after the active phase of the disease had subsided, no alterations from normal, except for slight slowing of the sinus rate could be produced by the same experiment. They had returned to the state of reactivity which characterized normal hearts checked by this method.

If this work is substantiated by additional studies, it would appear to offer a means of sensitizing our technique for the detection of cardiac involvement in rheumatic fever. We do not as yet know whether other

TABLE I (From Wendkos)

CHANGES IN THE ELECTROCARDIAGRAM FOLLOWING THE ADMINISTRATION OF ERGOTAMINE

Case No.	*Age*	*Date*	*Response to Ergotamine*	*Remarks*
1	24	2-14-44	Second degree A-V heart block with dropped beats	Rapid sedimentation time Joint pains present
1	24	3-25-44	Some slowing of sinus rate	Normal sedimentation time Joint pains absent
2	21	1-24-44	Nodal rhythm with first degree A-V heart block	Rapid sedimentation time Acute polyarthritis
2	21	3-1-44	Some slowing of sinus rate	Normal sedimentation time Joint pains absent
3	19	12-10-43	First degree A-V heart block (PR-0.28)	Rapid sedimentation time Acute polyarthritis
3	19	3-10-43	Some slowing of sinus rate	Normal sedimentation time Joint symptoms absent
4	21	3-12-44	First degree A-V heart block (PR-0.40)	Rapid sedimentation time Joint pains both shoulders
4	21	3-23-44	Some slowing of sinus rate	Sedimentation time reduced Joint pains absent
5	19	3-12-44	First degree A-V heart block (PR-0.32)	Acute polyarthritis Sedimentation time rapid
5	19	3-18-44	Some slowing of sinus rate	Arthritis completely disappeared Sedimentation time reduced
6	34	1-3-44	First degree A-V heart block (PR-0.30)	Sedimentation time rapid. Acute polyarthritis with some persistent deformity and swelling in small joints of hand

infectious diseases can produce a similar reaction, or whether such a reaction can be elicited during the toxic period of the first, or upper respiratory phase of rheumatic fever.

It has previously been demonstrated that a parasympathicolytic drug such at atropine can temporarily abolish the first degree A-V heart block and other types of rhythm disturbances, which are the chief electrocardiographic expressions of the disease. This work with ergotamine tartrate suggests that subordination of a hypervagotonic state below a critical level will prevent the registration of the usual electrocardiographic pattern of this dysfunction. The depression of the normal antagonist of the vagus by the use of a sympathicolytic preparation

such as ergotamine tartrate may permit the latent phase to register existing changes in the electrocardiogram. Further studies of this phenomenon may yield worthwhile information and aid us to evaluate more accurately the extent of involvement of the heart during the acute phase of the disease. The degree of *permanent* damage in mild cases still eludes our best efforts.

Other transient changes in the electrocardiogram have been frequently observed. These include inversion of the QRS complex and diminution or inversion of the T wave, especially in lead 4. Serial electrocardiographic studies revealing elevation of all or most of the S-T segment, followed by inversion of T waves in multiple leads have been suggestive of pericarditis with an active inflammatory process in the subepicardium. In 18 per cent of a series upright T waves exceeding 10 Mm. occurred in lead CF_4.[7] Wandering pacemakers were encountered in a small number of cases.

The Chemotherapeutic Aspects of the Treatment of Rheumatic Fever

While no completely satisfactory therapy is available for rheumatic fever, the attack has been actively pressed in the military hospitals. Penicillin is now recognized to be of no value in combating this disease.[8,9] The therapeutic use of the sulfonamides has likewise been disappointing. The prophylactic use of sulfonamides will be discussed below. The streptococcus antisera have been without value.

The most interesting contributions to therapy have dealt with the use of salicylates, which have entertained varying degrees of popularity during the past years. A very definite step forward was taken by Brodie, Udenfriend and Coburn in establishing a method for determining the level of salicylic acid in the plasma.[10] This at least makes it possible to be certain that adequate absorption takes place by whatever method of administration is used. While there may be some correlation between the level of salicylates in the plasma and the therapeutic response, there is a considerable variation in this which may be due to (a) a difference in response of the antigen or the inflammatory reaction in different hosts, (b) to the possibility that the level in the blood may not always bear a direct relationship to the level, or utilization in the affected tissues themselves. Further work will help to clarify this point.

The use of larger doses of salicylates orally and intravenously has

been advocated by Coburn and others. This has stimulated more careful observations of the use of these large doses and certain facts and questions have evolved. We have found that most of our patients can tolerate, without serious inconveniences, doses of salicylates which we formerly hesitated to prescribe. A dose of 6 to 8 grams daily was formerly considered to be a large dose. Coburn suggested 10 gms. (150 grs.) as an average, seeking to maintain a level of 35 mg. per 100 cc. or higher. I have seen 20 gms. (300 grs.) given daily to certain patients without detectable untoward effects. Perhaps this tolerance for the drug is related to the splendid physical condition of the men at the onset of the disease and to the diets which they have received containing adequate vitamin K. At present, this must remain speculation. The problems of salicylism will be discussed later.

Agreement has been reached regarding the value of salicylates administered orally, but the determination of additional value following intravenous administration is still debated. The action of salicylates is, in all probability, not upon the infectious agent but rather upon the sterile inflammatory reaction which occurs during activity of the rheumatic process. The evaluation of therapeutic response is determined by clinical improvement and the curve of the sedimentation rate which is generally accepted as being of great value in following the course of this disease.

Early reports suggested that the administration of 10 gms. of sodium salicylate per day intravenously for 6 to 8 days followed by the oral administration of equal doses would result in a rapid subsidence of clinical activity and a drop in the sedimentation rate to within normal within fourteen days. Most of our patients have responded very well clinically to rest in bed and from 10 to 12 gms. of salicylate daily without intravenous therapy.

The evidence at present seems to indicate that intravenous administration has no advantages over oral administration, with the possible exception of rapidity of rise in the blood level. If this route is to be used at all, salicylates should be given intravenously only to very acutely ill patients and patients with evidence of early pericarditis. There is considerable doubt that it is ever necessary.

The response of the sedimentation rate to both intravenous and massive oral dosage has been disappointing having, in a large proportion of our patients, failed to approach normal until the third to the

sixth week of the treatment. This lag has occurred in spite of blood levels of 35 mg. per 100 cc. or more.

The use of the large dose technique with blood levels of 35 mg. or higher does not offer complete protection against pericarditis. I have seen four patients who developed pericarditis during intravenous therapy.

Comparable series were studied in one hospital with the intravenous technique (10 gms. daily) followed by 10 to 16 gms. orally of sodium salicylate daily and with oral administration alone.

Of twenty-nine patients treated initially by intravenous technique, six had probable or definite heart disease before this attack (based on a history of rheumatic fever and presence of a cardiac lesion). Twenty developed evidence of a cardiac lesion during the period of observation as judged by either progressive electrocardiographic changes or the development of what were considered to be significant murmurs. Nine did not. Five of the new patients showed persistent evidence of cardiac residua in the form of significant murmurs. Eleven showed no residua. On thirteen, the late follow-up was unsatisfactory.

Of twenty-nine patients treated throughout by oral administration of 10 gms. daily, seven had cardiac disease before the present attack, eighteen developed signs during this episode, five of these showed persistent cardiac residua, nineteen showed none, and on five, the follow-up was unsatisfactory. In reference to cardiac lesions, the results were, therefore, not strikingly different in these small series.

While there exists serious doubt regarding the merits of intravenous over oral methods of administration, there is practically universal agreement that massive dosage (10 gms. or more) given by either route has produced more uniformly satisfactory palliative results than the smaller doses formerly employed. Many patients can be cited in whom the clinical course including the sedimentation rate improved strikingly with elevation of the plasma salicylate level but in whom the relapses occurred when the plasma level was allowed to drop below 20 mg. per 100 cc. Sharp evidence that this problem is far from solved was presented by one series of sixty-four patients receiving massive dosage therapy by mouth of whom twenty-nine or 45 per cent developed persistent valvular heart lesions.

One of the complications which has been more prominent following the use of such large doses of salicylates is acute salicylism. Some patients

can tolerate levels of 60 mg. per 100 cc. without symptoms but many of our patients develop mild symptoms at a level between 25 and 35 mg., and the percentage increases with the elevation of the level. Beginning with tinnitus, colored vision, nausea, and vomiting, this may progress to a more severe phase of which hyperventilation is a warning signal. This may increase in depth and intensity to simulate Kussmaul breathing. This hyperpnea produces a respiratory (paradoxical) alkalosis which results in lowered CO^2 content of the serum, loss of base (sodium) from the serum via the urine; retention of chloride in the serum; decreased renal function with retention of water, numbness, tingling of extremities, and tetany with carpopedal spasm and positive Chvostek's sign. An acute maniacal delirium may accompany this picture or develop as an isolated reaction.

Mild or moderate salicylism is not of serious significance. If severe with a serum salicylate level of under 50 mg. per 100 cc., one or two liters of normal saline intravenously with sodium bicarbonate, 0.6 gms. every four hours by mouth is usually adequate. If the level is over 50 mg. the salicylate should be stopped and one to five liters of normal saline given intravenously slowly. This toxicity can be prevented in practically all cases by a dose of 0.9 gms. of sodium bicarbonate with each dose of salicylate.[11] On the other hand, it has been shown by Smull, Wégria, and Leland,[12] that the administration of therapeutically satisfactory doses of sodium bicarbonate definitely decreases the level of salicylates in the blood. We must apparently, by balancing the administration of these two substances, tread between the maximum therapeutic effect and the toxic level, and this zone may differ considerably in different individuals.

For the reasons presented above, salicylic acid cannot be considered the final solution to the therapeutic problems occurring in rheumatic fever. The objectives can be clearly stated. A drug must be found which: 1) is non-toxic in effective therapeutic doses, 2) modifies the immune response of the host so that the patient recovers promptly after a monocyclic attack, or 3) inhibits the capacity of the infecting micro-organism to elaborate antigen. In the absence of fulfillment of any of these objectives we are limited at present to the action of the salicylates in suppression of the inflammatory process.

The possibility of prophylaxis of rheumatic fever with sulfonamides has been the subject of much thought and study. These drugs are of no

value in the treatment of the acute phase of the disease. Figures have been presented on numerous occasions supporting the thesis that small doses of sulfanilamide (0.5-1.0 gm.) taken daily will markedly decrease the incidence of recurrences of rheumatic fever after the first attack. Statistically, some of these figures have been subject to question.

Some of the patients have now taken this dosage for several years. This interminable program is not feasible as a preventive measure for use with groups of thousands of troops merely because they happen to be located in an area with a high rate for rheumatic fever. Methods have been used whereby varying dosages have been administered, i.e., 4 gms. sulfadiazine in 48 hours, 6 gms. in 72 hours, and 1 gram daily for a period of weeks. The rates of upper respiratory diseases can apparently be very favorably affected,[13] especially by the last named dose. This can be anticipated in those that are associated with streptococcus infections.

Scarlet fever and meningococcus infections are likewise favorably affected by the sulfonamides prophylactically. The evidence for the long-term effect on rheumatic fever of these small doses over short intervals is to date suggestive,[14] but less conclusive and must await further work.

Fear has been expressed that the early use of sulfonamides after the acute phase of rheumatic fever might unfavorably affect the course of the disease even causing relapses. Under our direction one gram of sulfadiazine has been given to each of twenty-five patients daily for twenty-one days beginning on the fifth day after the temperature had reached normal, regardless of the level of the sedimentation rate. In no instance was any elevation of the sedimentation rate or change in symptomatology noted which could be attributed to the administration of the sulfadiazine; therefore, although the possibility cannot be denied, it seems that risk on this basis is probably not excessive. Further studies on this problem are being carried out. The risk of sulfonamide sensitization must be considered in mass treatment. After sensitization has occurred, skin reactions are not uncommon and we have seen two acute deaths which appeared to be of an anaphylactic nature.

Comments and Conclusions

Rheumatic fever, as it occurs in the Army, has been demonstrated to be a manifestation of a highly communicable disease complex which

frequently is preceded by an outbreak of upper respiratory infections. Evidence is accumulating that it is an anaphylactic reaction, probably to the streptococcus Group A. This is not, however, conclusively established as yet. It may be widespread in its attack on well-nourished young men believed to be in excellent physical condition. The greatest involvement has been among the *younger groups* of servicemen. Fatigue, exposure to cold and dampness, and close living quarters are believed to be important environmental factors. Patients with a previous history of rheumatic fever are especially susceptible to recurrences when exposed to the rigors of military life.

The symptoms, physical findings, laboratory and electrocardiographic changes have been presented. The rarity of subcutaneous nodules, purpura, and chorea is of especial interest. The occurrence of prolongation of the P-R interval and of Aschoff bodies in the hearts of patients with "so-called" typical rheumatoid arthritis of many years standing has been confirmed. The possibility of sensitizing our methods of determining latent damage to the conduction mechanism of the heart by the use of ergotamine tartrate has been discussed.

The present status of the treatment of rheumatic fever remains unsatisfactory. Penicillin and the sulfonamides have been proven to be valueless in the treatment of this disease. There is no evidence that penicillin is of value as a preventive. Prolonged daily dosage of sulfanilamide appears to lessen the frequency of recurrences.[14] The evidence that short courses of sulfonamides are of long term value in the prophylaxis of primary or recurrent attacks of rheumatic fever is suggestive, but not as yet conclusively established. It is possible to markedly reduce the rate of upper respiratory infections, especially those associated with certain strains of streptococci by this method.

A step forward has been taken in the treatment of rheumatic fever with the development of a method for determining the level of salicylates in the blood thus aiding in the control of the dosage. It is fairly well agreed that large doses of sodium salicylate, i.e., 10 gm. daily or more are more rapidly palliative than the formerly used smaller doses. It is highly doubtful that the intravenous administration of salicylates is of greater value than oral administration. The clinical response to large doses has been rapid, but the response of the sedimentation rate has in many of our cases been disappointingly slow. The use of the massive dose methods does not offer complete protection against pericarditis,

myocarditis, or endocarditis.

With massive doses salicylism must be watched for. It can be prevented by giving sodium bicarbonate with the sodium salicylate, but it should be appreciated that this will result in a lowering of the blood level of the salicylates. The effect which this may have on the efficiency of the salicylates has not been established.

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CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

MAY 16, 1945

MEDICAL DIVISION

BERNARD S. OPPENHEIMER, *Chairman*

* * *

Electrocardiographic Changes During Intravenous Therapy of Pneumonia

DAVID D. RUTSTEIN, K. JEFFERSON THOMSON and DANIEL M. TOLMACH

Evidence has previously been published* that certain reactions to the intravenous administration of antipneumococcus serum are not due to anaphylaxis but are a response of the circulatory system to reaction-producing materials contained in the preparation of serum used.

As an outgrowth of this study, an investigation was performed on the changes in the electrocardiogram occurring during the intravenous administration of antipneumococcus serum and the sodium salts of the sulfonamide drugs.

Significant electrocardiograph changes occurred in 16 of the 112 injections of antipneumococcus serum in 59 pneumonia patients and in 3 of the 32 injections of sodium salts of sulfonamide drugs in 24 pneumonia patients.

Striking changes occurred in serial electrocardiograms in 3 patients, in one of which the changes are indistinguishable from those associated with acute myocardial infarction and 2 of which are suggestive of severe myocardial damage. One of these patients received Type 1 antipneumococcus horse serum, another Type 8 antipneumococcus rabbit serum, and the third sodium sulfathiazole.

* "Immediate Serum Reactions in Man," Archives of Internal Medicine, Vol. 68, pp. 25-56, July 1941.

* * *

Streptomycin in the Treatment of Typhoid Fever

HOBART A. REIMANN, ALISON H. PRICE and WILLIAM F. ELIAS, Ph.D.*

From the Jefferson Medical College and Hospital, Philadelphia

Streptomycin, an antibiotic substance derived from Actinomyces griseus, is bactericidal for E. typhosa in amounts of 4 to 6 units per cc. of broth. These amounts can be easily attained or exceeded in the body by intramuscular or intravenous injection of from 1 to 4 million units daily; they can also be attained in the stool by oral administration of similar amounts.

Five patients with typhoid fever were treated, 3 intramuscularly, 1 intravenously and in 1 both orally and intravenously. They received from 9 million to 30 million units. No beneficial effect occurred in 1, but recovery accompanied therapy in 3. In another patient treated intravenously, the temperature was falling when the supply of streptomycin was exhausted. The temperature rose to high levels again.

Streptomycin can be attained in the body in amounts which are theoretically adequate to kill E. typhosa. In 5 treated patients, recovery was synchronous with therapy in 3. There is reason to believe that the drug will also be of value in infections caused by other pathogenic gram-negative bacilli.

* From the Wyeth Institute of Applied Biochemistry, Philadelphia.

*The Clinical Response in General Paresis to Treatment with Penicillin**†*

EDWIN J. DOTY, HERBERT KOTEEN and WALSH MCDERMOTT

In a series of 115 neurosyphilitics who were treated with penicillin, only eight patients presented unequivocal evidence of general paresis. Satisfactory therapeutic results, as judged by physical, psychiatric and laboratory examinations, were observed in four of the eight patients during a follow-up of six to twelve months. With one exception, the observed improvement was not so marked as is usually seen at a comparable interval after malaria therapy. Two patients with advanced paresis failed to improve after 9,000,000 and 18,000,000 units of penicillin, respectively.

The results of this preliminary study would indicate that although intensive penicillin therapy exerts a definite beneficial effect on the mental, physical and laboratory abnormalities of general paresis, the extent of this beneficial effect, at least with the present dosage, is not so satisfactory as that following malaria.

* From The New York Hospital, and the Departments of Medicine and Psychiatry, Cornell University Medical College, New York.

† Work done under contract with the Office of Scientific Research and Development.

* * *

Objective and Clinical Study of the Normal, Desquamated and Atrophic Tongues

JOSEPH R. DIPALMA

The purpose of this study is to place upon an objective basis the clinical observation of changes in surface contour of the tongue in certain diseases, particularly the anemias and the avitaminoses.

By the development of a special ink which is tasteless, non-poisonous, of the proper consistency, and fast drying, it has been possible to make accurate prints of the tongue. When studied under the low power microscope it is possible to not only count the relative populations of the filiform and fungiform papillae but also to make observations on the surface contour of the mucous membrane of the tongue. Study of over 100 normal adults in the third decade of life has established the average surface contour and papillae count of the normal tongue.

Comparison of the normal tongue prints with those in disease conditions has revealed the following: People with a poor dietary history show a marked tendency to desquamation of the filiform papillae, especially with acute systemic infections such as pneumonia. However, the underlying fungiform papillary structure remains intact. Recovery quickly takes place with vitamin therapy. In advanced avitaminosis and in senile atrophy of the tongue both filiform and fungiform papillary structure disappears. Recovery, if it occurs at all, is very slow.

In the anemia group, pernicious anemia is distinctive because of the tendency of the tongue to show longitudinal ridging during the relapse, the so-called "scrotal pattern." The hypochromic anemias, when severe, show the most marked flattening of surface pattern. Even in these tongues recovery can be demonstrated with specific therapy of the anemia and with vitamins.

On the basis of these observations a plea is made for modification of the clinical term, "the smooth tongue." While this term is descriptive it fails to indicate exactly the change in surface contour. By the simple method here described it is possible to state accurately that the tongue is either just desquamating or is going on to atrophy of papillary structure.

The Modified Insulin Technique in the Treatment of Ambulant Psychiatric Patients

RICHARD M. BRICKNER

1. The ambulant insulin treatment method of Polatin, Spotnitz and Wiesel has been employed in 26 cases of different types.

2. The symptom of intense tension can usually be relieved, in whole or in part, by this treatment.

3. This series also adds a small amount of evidence to that more extensively accumulated by others, that the basic illness may be relieved by this method. This applies to schizophrenia and to depression.

4. The treatment may be given either in occasional isolated doses or as a systematic procedure with increasing doses, extending over a period of weeks.

5. The treatment is feasible for office use. After the injection has been given, no special set-up is required beyond the presence of a trained person to watch the patient and the presence of the doctor in the office.

6. The dosage ranges are far lower with the subcutaneous than with the intravenous route of administration.

7. The treatment cannot be used in the office with psychotic patients unless the manifestations are symptomatically mild. Patients should be hospitalized instead, if there is any question of risk in keeping them unhospitalized.

* * *

Personality Reaction to Crime and Disease

DAVID ABRAHAMSEN

Research Associate, Department of Psychiatry, Columbia University

This psychosomatic study, supported by the Josiah Macy Jr. Foundation, is a preliminary report of a clinical research project about the individual's personality reaction to his diseases and to his antisocial acts. Various types of conflicts may in due time lead an individual either into neurosis, psychosis, a psychosomatic disorder, or a criminal act. The question then is, *how* does a person react to his disease, and to an antisocial act of his own commission? The personality make-up present in the person determines how he will react when affected with a bodily disease and what form a maladjustment will assume. As the reaction to the illness depends upon what the personality was before the onset, so also the individual's reaction to his antisocial act is dependent upon his personality traits before the antisocial act was committed.

From a group of offenders, two typical ones are selected for detailed description. Both experienced a childhood with deprivations; during adolescence they went through prolonged periods of physical ailments which seemed to be tied up with their personality traits and with their antisocial acts. Results of physical examinations and laboratory tests are given. Conclusions are drawn as to presence and incidence of some factors in the etiology of the individual's antisocial behavior and the nature and course of his disease and compared with the incidence of psychosomatic disorders in patients suffering from neurosis or psychosis.

A Comparison of Several Special Preparations of Protamine Zinc Insulin in the Treatment of Diabetes Mellitus

HENRY DOLGER

Twenty-five patients with severe diabetes mellitus who had been treated more or less satisfactorily with extemporaneous mixtures of insulin and protamine zinc insulin were studied. They were given three different fixed modifications of protamine zinc insulin specially prepared by the Research Laboratories of the Eli Lilly Company. Two modifications were acid clear and contained either 1.25 or 1.75 mgs. of protamine per 100 units. The third was neutral (cloudy) and contained 0.42 mgs. protamine per 100 units or one-third that found in commercially available protamine zinc insulin (i.e. 1.25 mgs.). The latter, therefore, resembled a mixture of two parts regular to one part protamine zinc insulin prepared extemporaneously.

The acid preparations were found to be similar to globin insulin in that late afternoon hypoglycemic reactions and severe early morning glycosuria were noted. The neutral preparation was more satisfactory by providing a smooth control of glycosuria and freedom from both afternoon and early morning insulin shocks. In fact this modification afforded even better results than the original extemporaneously prepared mixtures.

* * *

On the Significance of Nutritional Deficiency in Diabetes

MORTON S. BISKIND and HERBERT SCHREIER

From the Endocrine and Diabetic Clinics, Beth Israel Hospital and the Diabetic Clinic, Gouverneur Hospital

Soskin and his collaborators,[1] in a brilliant series of investigations, have demonstrated the basic role of the liver in maintaining normal carbohydrate balance and have supplied abundant evidence that diabetes may often be a disease of the liver. Among other experiments, they have shown that damage to the liver by toxic agents produces the diabetic type of dextrose tolerance curve. It is now well known, through the work of many investigators, that nutritional factors, especially those of the B complex, protect the liver from both the functional and structural impairment which results from a variety of toxic agents; it has also been shown that the hepatic impairment which occurs from the latter, results from a secondarily-induced deficiency of the nutritional factors.

Among the functional impairments which result in the liver from primary or secondary deficiency of the vitamin B complex, is the failure of inactivation of estrogen,[2] with the production of clinical syndromes associated with excess estrogen (menometrorrhagia, cystic mastitis, premenstrual tension, uterine myomas, postpartum subinvolution of the uterus, etc.). Thus, a series of conditions, thought formerly to be purely endocrine, have been shown to result from impairment of hepatic function on a nutritional basis.[3] Nutritional therapy in these conditions has produced striking improvement.

On the basis of these and related findings, for more than two years we have been investigating the occurrence of nutritional deficiency in diabetics; and on the basis of past experience in treating other syndromes related to hepatic dysfunction, we have studied the results of intensive therapy with the vitamin B complex in these patients. We have been impressed by the virtually universal occurrence of signs and symptoms of nutritional deficiency in diabetics; by the striking improvement in

general health and well-being which occurs on adequate oral or oral and parenteral vitamin B complex therapy; and by definite improvement in carbohydrate metabolism, often permitting a reduction in the insulin requirement, or its elimination altogether. In addition, patients requiring insulin had less difficulty with insulin reactions. In several cases in which marked improvement occurred with B complex, a definite correlation was possible between the occurrence of the hepatic dysfunction and the development of the diabetic state.

Experimental support of our findings in the human being has just been published by Gaebler and Ciszewski,[4] who demonstrated that in experimental diabetes in dogs, the diabetic state was markedly worsened and the insulin requirement was greatly increased by deprivation of the B complex. Addition of B complex to the diet restored the former carbohydrate equilibrium.

Our clinical observations, as well as the experimental investigations mentioned, suggest strongly that nutritional deficiency is of etiologic significance in diabetes. From the standpoint of practical therapy, this concept has proved extremely valuable.

Lesions of nutritional deficiency occurring in diabetics are illustrated in kodachrome.

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The Effect of Bed Rest and Immobilization upon Physiological and Chemical Functions in Normal Men

JOHN DEITRICK and DONALD WHEDON*†

Two healthy young men were studied during an eight weeks control period while on a regular exercise routine. They were then put to bed for six weeks in a bivalved cast reaching from the feet to the umbilicus. Following this period, observations were made during a four weeks recovery period. Diets were held constant throughout the entire experiment.

SUMMARY

1. A definite increase in nitrogen, calcium and phosphorus excretion occurred on bed rest. Sulfur and potassium execretion increased slightly. The maximum calcium excretion follows the maximum nitrogen excretion by approximately two weeks.

2. No correlation could be established between nitrogen excretion and 17-ketosteroid excretion.

3. In spite of increased calcium output there were no corresponding changes in pH and citric acid excretion which would increase the solubility of calcium.

4. Although there was immobilization of approximately half the body musculature no change in creatine excretion occurred. The creatine tolerance however did diminish on bed rest.

5. The most striking changes in functional studies were the loss of strength and the progressive failure of the circulation in response to the upright position.

* From the New York Hospital and Cornell University Medical College Department of Medicine, and the Russell Sage Metabolism Ward.

† This work was undertaken through contract with O.S.R.D. under the direction of the Committee on Convalescence and Rehabilitation of the N.R.C.

* * *

*The Rationale of Sodium Salts in the Treatment of Shock**

CHARLES L. FOX, JR.
Department of Bacteriology, College of Physicians and Surgeons, Columbia University

Recent studies by Richards support the view of Cannon and Wiggers that "reduction in the volume of blood returned to the heart is the keystone of all modern conceptions of shock." To discover the mechanism of shock it is then necessary to ascertain the cause of the "reduction in the volume of blood returned to the heart." The commonly accepted hypothesis is that of Blalock that "the decrease in blood volume could be entirely accounted for by the amount of blood or plasma lost at the site of local injury."

Since Blalock's studies in 1930, Gamble, Peters, Hastings and their associates have made important contributions regarding the chemical composition and distribution of body fluids. It was then found by Darrow and Yannet in animals, by Loeb, Harrop and Swingle in Addison's disease and by McCance after experimental salt deficiency in man that *external* loss of body sodium *without loss of plasma* resulted in reduction of blood volume, hemoconcentration, decrease in circulating plasma proteins, circulatory failure and typical "shock."

In shock following experimental burns, trauma, or hemorrhage, Rosenthal then demonstrated[1] the therapeutic efficacy of large volumes of isotonic solutions of sodium salts; "that the curative effects of serum are due to its electrolyte content"; that concentrated albumin is without effect.

Clinical trial in 112 patients with burns[2] and 30 patients with shock from trauma and hemorrhage[3] showed the benefit of oral and intravenous administration of volumes of isotonic solutions of sodium salts equal to 10 to 15 per cent of body weight. It is encouraging to note that the latest recommendations of the Shock Committee of the National Research Council advise a total volume of 8 to 15 liters of fluid (including some blood or plasma) in the first 24 to 48 hours after injury.

The rationale for the sodium therapy of shock is explained by quantitative analysis of the chemical changes in tissues following severe trauma. These data were obtained by analyses with radiosodium,[4] radiopotassium, and direct analytical methods totaling 2500 determinations. The results may be summarized as follows:

1. Large amounts of sodium and water accumulate in injured tissues; the gain in sodium exceeds the gain in water.

2. The potassium content of injured tissues is reduced; the decrease in potassium approximating the "excess" of sodium. This indicates breakdown of cell barriers with an exchange of extracellular sodium for intracellular potassium.

3. The protein content of injured tissues is *not* increased above that of contralateral uninjured tissues. Protein found in the edema fluid apparently is derived from the damaged cells rather than from the plasma as is generally believed.

4. Uninjured tissues of the animal in shock lose sodium but gain potassium; their water content remains unchanged. This indicates intracellular edema with extracellular dehydration. The increased hematocrit in shock also results in large part from swelling of the red cells.

5. The therapeutic indication is to restore blood volume by replacement of the sodium and water of the extracellular fluid and plasma diverted and removed by these tissue changes.

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*Improved Technique for Preparing a Buried Dermal Graft in Hernial Repair**

JAMES V. SCOLA, 1st Lt., M.C., A.U.S.

This technique first is to denude the skin of the epidermal layer. Then the derma is cut away, making the graft of any desired size. This derma has subcutaneous fat attached to it, or if this is removed, the fibrous tissue at the base of the skin is attached to the graft. This subcutaneous fat or fibrous tissue on the undersurface of the skin offers a poor surface for a successful "take." The opposite side of the skin, however, (where the epidermal layer was removed) is an excellent surface for a successful "take." If the graft could be prepared so that both sides can take equally well, the chances of its viability are immediately doubled. It is the purpose of this paper to describe such a method.

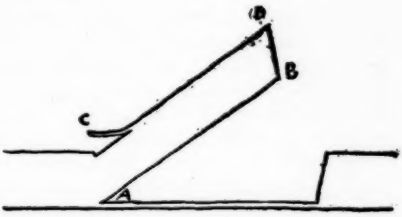

FIG. 1. This figure represents the full thickness of skin. Subcutaneous tissue is not shown. The first cut with the dermatome is from B to A, thus raising the almost full thickness skin flap as shown. The dermatome is now removed, set to cut a thin layer of skin (not over .008) and the cut is made from C to B as shown. The graft is now removed by cutting across at A.

Preoperatively, the thickness of the skin where the dermal graft is to be taken is roughly determined by gently pinching the skin. This is not difficult to do after trying it a few times. The peritoneum of the hernia is closed as usual and the fascial defect is measured. A dermal graft somewhat larger than the defect should be used.

Now the Padgett dermatone is set to cut a graft just short of the full thickness of the skin, thus leaving a very thin layer of epithelial cells on the donor site. This cut is usually between .04 to .05 inches, thus insuring a good thick graft. This graft is left attached at one end (A) as shown, cutting from (B) to (A).

The dermatome is now removed and reset to cut a very thin graft to remove the epidermal layer. This cut need not be over .008 inches (if the shellac used for the dermatome is made quite thin) and is made by cutting from C to D. Allis forceps are used to spread the graft until it is stuck to the drum of the dermatome. When the dermatome is used for the second cut, the old shellac must be removed from the drum and new shellac applied to the drum and skin. The old shellac need not be removed from the skin.

The dermal graft is now removed by cutting it across at A. The graft is sutured to good fascia surrounding the defect, using interrupted silk sutures. A very light sprinkling of sulfanilamide powder may be applied over the graft if desired. The subcutaneous tissues are approximated over the graft, obliterating all dead spaces. The site where the graft was taken is covered with vaseline gauze and left undisturbed for seven to ten days.

A series of five cases is reported in four of which there was either no fascia to approximate or the fascia was too thin and frayed to be used for repairing.

* From the Graduate School in Surgery, New York Medical College and Flower Fifth Ave. Hospital. Presented by Joseph H. Fobes, Head of Graduate Surgery.

Therapeutic Effect of Radioactive Iodine on Adenocarcinoma of the Thyroid with Functioning Metastases

S. M. SEIDLIN and L. D. MARINELLI

This is a report on a patient, 52 years old, who had a complete thyroidectomy for a "malignant adenoma" in 1923. He had no thyrotoxicosis then nor hypothyroidism postoperatively. Fifteen years later, he developed classical symptoms of hyperthyroidism (B.M.R. + 40%) and severe pain in the lower back. In October, 1939, a pulsating tumor was removed from the level of the thoracic 12th and proved to be metastatic thyroid carcinoma (histologically, small follicles, well-differentiated with colloid). In the next two years, hyperthyroidism increased and x-rays revealed metastases in the lungs, right upper femur, second left rib, pelvis, and skull.

Deep roentgen therapy was ineffective. Lugol's solution therapy showed slight but definite effect on the hyperthyroidism. Geiger counter-studies after the administration of a tracer dose of radio-iodine demonstrated uptake by *all* the lesions. Thiouracil administration produced a typical remission of the hyperthyroidism, which recurred after cessation of treatment. Several massive doses of radio-iodine resulted in a striking improvement of the clinical picture: B.M.R. dropped to below normal; patient gained weight and there was a complete arrest in the growth of the metastases. Quantitative studies on the pick-up and excretion of the radio-iodine by the metastases were carried out. Thyrotropic hormone studies were also made.

* * *

*Pulmonary Suck and Blow as a Respiratory Analeptic; Interdependence of Cardiac Massage and Suck-and-Blow Resuscitation**

* From the Graduate School in Surgery, New York Medical College and Flower Fifth Ave. Hospital. Presented by Joseph H. Fobes, Head of Graduate Surgery.

JACOB REICHER

Based on Thompson and Birnbaum's demonstration of the "phenomenon of asphyxial resuscitation" by pulmonary suction and deflation (suck-and-blow), evidence is presented that combined suck-and-blow with cardiac massage serves as an effective resuscitant where either alone fails. Additional experiments are presented indicating that such a combination would be inadequate if the pulmonary ventilation consisted of either pressure alone or suction alone. It is emphasized that the application of suck-and-blow to the pulmonary tree does more than create an interchange of gases; the procedure serves as a true analeptic since it actually *stimulates* respirations mediated through nervous mechanisms. External methods of artificial respiration (manual, Drinker, Bragg-Paul, etc.) merely serve as substitutes for respiration; they do not stimulate.

A summary of the physiology of respiration is presented as it applies to suck-and-blow, and a résumé is made of the history of suck-and-blow devices. Asphyxia is discussed, as well as the arguments pro and con in the various methods of resuscitation including chemical analeptics in contradistinction to the reflex analeptic, pulmonary suck-and-blow.

*The Reaction of the Peripheral Circulation to Cold in Scleroderma, Raynaud's Disease and Thrombo-Angiitis Obliterans**

H. R. Miller, J. Marrus, M.S. and Beverly C. Smith

On the basis of results in acclimatization carried out on normal subjects in the Climatic Research Unit of the Signal Corps, Fort Monmouth, investigations were undertaken to determine the reaction of the circulation of the extremities exposed to intense cold in subjects with scleroderma, Raynaud's disease and TAO.

Cold normal digits revealed an ability to warm up spontaneously (phasic rise and fall in skin temperature). Warming could also be induced by temporarily occluding the circulation of the limb or by having the subject breathe CO_2 enriched mixtures.

The cold digits in the pathological conditions exhibited two types of reactions: (1) spontaneous warming, i.e., phasic rise and fall in digital skin temperature as in normal subjects; (2) a progressive rise in digital skin temperature which lasted several hours. The latter reaction especially was associated with increased tolerance to cold, diminution in pain, subjective sensations of warmth and comfort in the parts exposed to severe cold, and with signs of clinical improvement in some cases.

The investigations have demonstrated that in scleroderma, Raynaud's disease and TAO, it is possible to induce a marked and sustained increase in digital skin temperature. This response may have therapeutic value.

* From Columbia University College of Physicians and Surgeons.

* * *

The Functional Pathology of Experimental Frostbite and the Prevention of Subsequent Gangrene

Kurt Lange and Linn J. Boyd

The tissue alterations after exposure to severe cold were described and the sequence of events was illustrated by pathologic slides as well as kodachromes of fluorescein tests performed at different intervals after exposure.

Cold sufficient to solidify the exposed tissues causes a complete interruption of circulation during exposure. This is always followed by a period of complete restoration of circulation and increased capillary permeability as evidenced by the fluorescein test. This period lasts for 6 to 16 hours after exposure. This is the most promising period for therapeutic endeavors. The period of circulatory restoration is followed by one with arteriolar and capillary occlusion resulting from the formation of red cell clots. Gangrene of the associated area is the consequence.

Heparin administered during the period of circulatory restoration prevented gangrene in 16 rabbits whereas all controls had complete gangrene of the part. Five animals were exposed by freezing small areas. In the remaining animals the entire hind leg was frozen.

Although tissue loss was completely prevented by the early use of heparin, sensory and motor nerve paralysis was often not prevented.

A case of severe human exposure in which loss of tissue was to be expected was treated with heparin and gangrene was completely and successfully prevented.

Later experiments in human volunteers also showed the validity of this treatment in cases of human frostbite.

Heparin in the Treatment of Experimental Human Frost Bite

LEO LOEWE, KURT LANGE and PHILIP ROSENBLATT

The functional pathology of experimental frost bite in the rabbit has been elucidated by Lange and Boyd[1] through the medium of the fluorescein test. In the initial stages of frost bite there is merely clumping of erythrocytes in the small vessels due probably to loss of plasma through the highly permeable vascular walls. These stranded red cells which silt up the blood vessels forming a sludge do not, in the beginning, represent true thrombi. Organization into thrombi supervenes only after approximately 72 hours. They discovered that thrombosis and complicating infarctive gangrene after experimental frost bite could be prevented by heparinization, if started early.

Experiments were projected in human volunteers to (1) reaffirm the effectiveness of early heparinization, and (2) to develop a simple practical therapeutic program. For the latter, subcutaneous heparin/Pitkin Menstruum was the method of choice.

Experimental frost bite was induced in human subjects by applying to the skin the bottom of small porcelain crucibles filled with dry ice. The controls developed necrosis of the exposed area, while the adequately heparinized subjects, apart from superficial blistering of varying degree, escaped any deeper injury. Further experiments are in progress.

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DIVISION FOR PAPERS IN PATHOLOGY, SEROLOGY, BACTERIOLOGY AND PHARMACY

PAUL REZNIKOFF, *Chairman*

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Repository Injection of Penicillin in Water-in-Oil Emulsion: Effect on Gonorrhea

A. COHN, B. A. KORNBLITH, I. GRUNSTEIN, K. J. THOMSON and JULES FREUND

A study was undertaken to determine if penicillin injected intramuscularly is more effective in a water-in-oil emulsion than in aqueous solution. It was hoped that the absorption of penicillin might be prolonged by incorporating it in a water-in-oil emulsion so that the number of injections and perhaps the amount of penicillin could be reduced.

Single doses of water-in-oil emulsions of penicillin were prepared by a simple rapid-technique as follows: One and four tenths cc. of sterile 0.85 per cent salt solution are drawn into a sterile syringe and ejected into a vial containing 100,000 O. U. of dry penicillin. To the penicillin solution 3.1 cc. of an autoclaved mixture containing 11 parts of a lanolin-like substance (Falba) and 20 parts of peanut oil are added by means of a sterile syringe and a 17 gauge needle. With the needle still inserted through the rubber cap of the vial the mixture can be readily emulsified by repeated withdrawals and rapid reinjections

into the vial. As soon as the mixture assumes a uniformly creamy, slightly viscid consistency, satisfactory emulsification has occurred. The mixture is then ready for intramuscular injection.

Serum penicillin concentrations in patients with gonococcal infections after a single intramuscular injection of 150,000 O. U. of penicillin yielded detectable amounts of penicillin in a range of 2.5 O. U. per cc. within half an hour after injection to 0.008 O. U. per cc. 7 hours after injection. Corresponding determinations of urinary excretion of penicillin yielded appreciable amounts of penicillin as long as 28 hours after the original single injection.

The results of treating 52 patients with goncoccal infections by a single repository injection of 150,000 O. U. of penicillin were 50 cures and 2 failures. Forty-nine additional cases were treated by a single injection of 100,000 O. U. of penicillin in water-in-oil emulsion to which was added a "priming" dose of 50,000 O. U. of penicillin in aqueous solution simultaneously. No failure was observed in this group. No toxic side effects were observed; the local site of injection showed no untoward reactions.

* * *

*The Oral Administration of Penicillin in Normal Subjects and in Patients with Pneumococcus Pneumonia**

WALSH MCDERMOTT, PAUL A. BUNN, MARIA BENOIT, REBECKAH DU BOIS and WILLETTA HAYNES

Department of Medicine, Cornell University Medical College and New York Hospital

The oral administration of penicillin by a number of methods, which have included the use of oil, oil and beeswax, aqueous solution preceded by a buffer, and aqueous solution alone, has been investigated in a series of normal subjects and patients with pneumococcus pneumonia. It was concluded that:

1. It is possible to attain blood penicillin concentrations after administration comparable to those attained after intramuscular administration by the use of approximately five times as much penicillin.

2. As the concentrations attained in the blood, and the amount excreted in the urine following the ingestion of penicillin in four different vehicles including water were all of the same order of magnitude, it would seem that none of the vehicles studied protected the penicillin from destruction in the body and that the absorption which occurred was merely a reflection of the amount of penicillin which was ingested.

3. The therapeutic results attained following orally administered penicillin to forty patients with pneumococcus pneumonia were comparable to those observed after intramuscular therapy and were equally satisfactory whether the penicillin was administered in oil, in water, or as the dry powder in a capsule.

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University.

Subclinical Trichinosis. A Clinical and Pathologic Study

S. E. GOULD
Eloise Hospital

A surprisingly high incidence of trichinous infection (as high as 29.3 per cent, according to the method of examination used) was found in persons coming to autopsy at Eloise Hospital, the county hospital of the Detroit area. A study was undertaken to determine the value of intradermal and precipitin tests and eosinophilic cell counts in the diagnosis of old subclinical trichinosis. The results of these tests made during life were correlated with the presence or absence of *Trichinella spiralis* in those persons who had been clinically tested and who later came to autopsy.

Of 3501 patients who had been skin-tested with trichina antigens, 388 were examined for trichinellae at autopsy; of 548 who had had blood precipitin tests, 66 came to autopsy and were examined for larvae; while 886 patients who had had eosinophilic cell counts during life were similarly investigated for trichinae post mortem. It was found that the trichina intradermal and precipitin tests and the eosinophilic cell count cannot be relied upon to indicate the presence of old subclinical trichinosis. Eosinophilia usually persists 6 months and rarely more than a year after infection. It is believed that the blood precipitin test remains positive for 1 or 2 years and that the immediate type of intradermal reaction may be elicited, on the average, for nearly 10 years after infection. The immediate intradermal test was found to be more sensitive and easier to read than the delayed intradermal test. About 5 per cent of reactions obtained with the immediate intradermal tests were non-specific in nature and were believed to be possibly due to sensitization induced by antigenic material in non-viable trichinae present in ingested pork. The possibility of obtaining either non-specific intradermal reactions, or specific reactions from previous trichinous infection, should be remembered in testing patients with suspected clinical trichinosis.

* * *

Methods for Achieving Optimum Penicillin Blood Levels Including the Use of Enhancing Agents Such as Para-Aminohippuric Acid

LEO LOEWE, PHILIP ROSENBLATT and ERNA ALTURE-WERBER, Ph.D.

This study was undertaken to determine optimum penicillin dosages in patients with subacute bacterial endocarditis who were refractory to treatment, and also, those infected with Streptococcus s.b.e. In view of ineffective penicillin blood levels obtained with standard dosages in these resistant patients, it was necessary to employ huge amounts of penicillin before achieving therapeutic levels. Because of the non-toxic character of the presently available penicillin, dosages up to thirty million Oxford units per day were administered by continuous venoclysis. The uninterrupted flow of this massive dosage, which was well tolerated, was made possible only by the conjoint use of heparin. Continuous intramuscular administration could not be employed because of the severe pain, local reaction and fever induced. Blood levels of 60 Oxford units per cc. were obtained. To conserve penicillin, enhancing agents such as para-aminohippuric acid were successfully employed in some experiments. The clinical importance of these results is evident in connection with resistant organisms in subacute bacterial endocarditis and also in the management of the group of diseases caused presumably by penicillin insensitive types of organisms.

Sudden Deaths in Infancy

JACOB WERNE and IRENE GARROW

The investigation of sudden deaths during infancy has, in the past, been relatively unsatisfactory. These cases have usually been certified as due to accidental mechanical suffocation if the subject has been found dead in the crib, or as status thymicolymphaticus if the death occurred under other circumstances and still remained unexplained at autopsy.

The authors have been studying this problem for the past 14 years in the Office of The Chief Medical Examiner, Borough of Queens, and conclude that the sudden death of an infant, unexplained by gross findings at the autopsy table, will, on further investigation (microscopic, bacteriologic and epidemiologic), prove to be an expression of fulminating infection, usually respiratory in origin.

This presentation summarizes the completed study of some 200 cases, including control material consisting of infants dying of trauma and of those dying of known respiratory infections.

* * *

An Investigation of Type Specific Meningococcic Agglutinins in Human Serum: II—Immunological Response of Proved Cases of Meningococcic Infection

CAROLYN R. FALK and EMANUEL APPELBAUM

Bureau of Laboratories of the Department of Health of the City of New York

The meningococcus agglutinin content of 252 bacteriologically proved cases of meningococcic infection was studied over a three-year period during which the incidence of this disease was high. Samples of serum were taken from the same patient from 1 to 34 times at intervals of from 1 to 21 days, and were representative of the acute, subacute, and convalescent stages.

Agglutinins in significant titers were found in 46 per cent of serums obtained during the acute, in 79 per cent of serums taken during the subacute, and in 68 per cent of serums obtained during the convalescent phase. The agglutinins appeared most regularly at the end of the first week of illness and reached a maximum titer during the second and third week. There was considerable individual variation as to the length of time that agglutinins persisted. The titers fell to pre-infection levels between the third week and the fourth month after onset.

Agglutinins for Group I, Group II, and Group II-alpha meningococci were found alone or in combination with each other. The agglutinins corresponded in prevalence with the type distribution of the infecting organisms. The type of the agglutinins found in the patients' serums corresponded with the homologous infecting organism in the 82 cases where both the infecting organism and the serum were available for study.

The agglutination test may be useful in determining the type of the infecting organism in cases where meningococci were not cultured from the blood or spinal fluid and in which the "Quellung" test was unsuccessful. This test may also be of value as an additional diagnostic procedure in cases of suspected meningococcic infection where other laboratory onfirmation is lacking. In this connection the importance of performing several tests to demonstrate the change of agglutinin titer cannot be overemphasized.

Morphological Studies of Salmonella Typhi Murium and Salmonella Enteritidis in Guinea Pigs and Mice

ALFRED ANGRIST and MOLLIE MOLLOV, B.S., M.A.

Above strains of salmonella organisms, recovered from human cases coming to autopsy, were fed to guinea pigs and mice, to note the morphological changes, particularly in the early stages. The source of the typhi murium organism was a case which came to autopsy with a typical picture of typhoid fever histologically.

One cc. of an 18-hour broth culture was fed to guinea pigs weighing between 250 and 300 grams, and ¼ cc. was given to 18-to-20-gram mice. Natural infection was ruled out before the feeding experiments. Infected animals were killed at varying periods, or when they appeared ill. Post mortem cultures and sections for histological study were taken of the heart, liver, spleen, nodes and intestine of the infected animals, as well as from the control group. In all cases, the original organisms were isolated from the infected group only.

The detailed morphological studies of the reaction in the Peyer's patch are presented. The exudative and proliferative changes, and the necroses selectively localized to such delimited areas of the gut (Peyer's patch) permit of the study of the early phases of bacterial invasion. The theoretical implications of the above morphological observations as to the mechanism of infection and of the necroses with sloughing and ulceration, as they apply to human paratyphoid and typhoid infections, are discussed briefly.

The reaction in Peyer's patches and the regional mesenteric lymph node tissue seems to be independent of the antigenic structure and to be contingent upon the relative general virulence of the organism and the resistance of the host, portal of entry and method of insertion in this instance. A parallelism with primary tuberculosis is drawn.

* * *

Oral Administration of Penicillin for Treatment of Gonococcal Infections

ALFRED COHN, BORRIS A. KORNBLITH and ISAAK GRUNSTEIN

Experimental observations of Schnitzer and Ercoli showed that mice infected with various organisms responded to oral therapy with penicillin.

They also found that when humans were given single doses of 120,000 O. U. of penicillin by mouth the blood serum levels varied between 0.05 and 0.4 per cc. within 1 hour and dropped to less than 0.001 within a period of 2 to 3 hours. When 240,000 O. U. were given, blood serum levels ranged between 0.1 and 0.4 O. U. within 1 hour and gradually dropped to 0.025 O. U. per cc. within a period of 3 to 5 hours. Two subjects receiving 120,000 O. U. and 240,000 O. U. respectively failed to show any appreciable blood serum penicillin level.

In view of these findings 40 patients with gonococcal infections were given oral penicillin therapy in tablet form. In a group of eleven patients 300,000 O. U. of penicillin were given in divided doses of 60,000 O. U. every 2 hours over a period of 8 hours. Another group of 29 patients received 600,000 O. U. in divided doses of 120,000 O. U. every 2 hours over a period of 8 hours.

Of the total of 40 patients treated, 30 were cured and 10 failed to respond to this form of therapy. The percentage of failures in each group was practically the same. No toxic side effects were observed.

Experimental Study on the Activity of Penicillin Administered Orally in Experimental Streptococcus, Pneumococcus, and Meningococcus Infection of Mice

R. J. Schnitzer, N. Ercoli, D. J. Longacre and G. Soo-Hoo, M.S.

In large series of experiments, it was shown that sodium penicillin administered orally in aqueous solution exerts a striking therapeutic effect in all experimental infections which respond to the parenteral administration of penicillin. A comparison of the dosage required to protect at least 60 per cent of the intraabdominally infected animals showed that the ratio $\frac{\text{minimal oral dose}}{\text{minimal subcutaneous dose}}$ varies with the different infections.

In infections with the very sensitive β-hemolytic streptococci and with pneumococci type 1 and type 2, this ratio was 10, indicating that a 10 times higher dose of penicillin was required by the oral route. Infections with Staphylococcus aureus and meningococci required higher doses for the subcutaneous treatment; and in these cases, the ratio: oral/subcutaneous-treatment became much smaller and was found to be not more than 2.5 for the staphylococcal and 1.0 in the meningococcal infection.

We found these observations confirmed in 3 more experimental infections which also could only be controlled by comparatively high doses (2000-4000 units) of parenterally administered penicillin: In infections of mice with Salmonella schottmülleri, with Borrelia novyi, and in the *intranasal* infection of mice with type 2 pneumococci, the ratio was 1.0 to 2.0.

Although the determination of the penicillin concentration in the serum allowed an interpretation of these findings to a certain extent, the effectiveness of penicillin treatment seemed to depend largely on the susceptibility of the infecting microörganism and on the defense mechanism of the host.

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The Proteolytic Activity of Serum and Plasma

L. R. Christensen, Ph.D. and Colin M. Macleod

The presence of proteolytic activity in serum and plasma has been known for many years. In general the activity is not demonstrable unless the serum has first been treated with chemical agents, such as chloroform and other organic solvents; organic compounds, such as urea and cresols; or unless the serum has been treated by dialysis or acidification. Recently it has been shown that the phenomenon of streptococcal fibrinolysis is due to the activation of a serum enzyme by streptococcal fibrinolysin.

Evidence will be presented indicating that the enzyme activated by fibrinolysin and that activated by other agents are identical. Characterization of this enzyme in regard to the effects of pH and temperature on its activity, and to the effect of certain specific protease inhibitors indicate that the enzyme differs from known enzymes and probably represents a specific protease, characteristic of serum. Data will be presented indicating that activation of the enzyme by streptococcal fibrinolysin is an enzymatic type of reaction, suggesting the conversion of the inactive enzyme or zymogen in serum to an active state by streptococcal fibrinolysin, a kinase, analogous to the enterokinase activation of trypsinogen.

A nomenclature is suggested for this serum enzyme system analogous to that used for other proteases. The active enzyme is termed "plasmin" to denote its origin, the plasma. The enzyme, as normally present in the blood, is termed "plasminogen" to denote its inactive or zymogen state. Fibrinolysin is termed "streptokinase" to denote its origin and action.

Certain implications of these findings will be discussed.

*The Use of Radioactive Sodium in Studies of Circulation in the Extremities**

BEVERLY C. SMITH and EDITH H. QUIMBY, Sc.D.

With the continually lengthening span of life, more persons live to develop degenerative arterial disease in the extremities. Pathological arterial changes alter circulation time, volume of blood circulating in the extremity, and relationship of plasma and extravascular fluid. Any means of obtaining information regarding these matters should be helpful in diagnosis and prognosis. We here report a method whereby intravenous injections of small amounts of radioactive sodium are used in circulation studies.

The radioactive sodium is obtained from the cyclotron laboratory of Columbia University; it is prepared in sterile saline for intravenous use. The disintegrating radioactive atoms are detected by a Geiger-Muller counting apparatus which gives an audible click for each disintegration.

The test is carried out as follows: The patient lies on his back, and the shield containing the Geiger-Muller counting tube is placed against the plantar metatarsal region of the foot. The desired amount of radiosodium is injected into an ante-cubital vein. The electric stop-clock and the injection being started simultaneously, the clicking of the counter indicates the arrival of the material at the foot, and the arm-to-foot circulation time is immediately established.

If the counter is kept in position against the foot, and counts are made each minute, the counting rate is found to increase steadily, quite rapidly at first and then more slowly. This is due to the interchange of sodium between plasma and extravascular fluid until equilibrium is reached between the two. The pattern of the build-up curve depends on the blood supply, the state of the vessels, and other conditions in the extremity. Circulation time and build-up pattern for normals have been established, and similar studies have been made in some 200 diseased individuals. These include fairly extensive series of patients with hypertension, arteriosclerosis, diabetes and thromboangiitis obliterans, and smaller groups with a wide variety of conditions.

When the main peripheral and collateral vessels are normal, the build-up pattern is that of the normal individual. If the main preipheral vessels are not palpable and oscillometric readings are absent or low, the rate of build-up largely measures the existing collateral circulation, and the nearer this approaches to the normal pattern the more adequately is the collateral circulation able to carry on the function of the impoverished main vessels.

These observations have been found to parallel closely clinical history and observation. They are now being used as a guide to therapy. In particular, a demonstration of adequacy of circulation in a projected amputation site has been of considerable aid in conservative surgery. Repetition of the test at intervals during or following therapy affords an estimate of the patient's progress.

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